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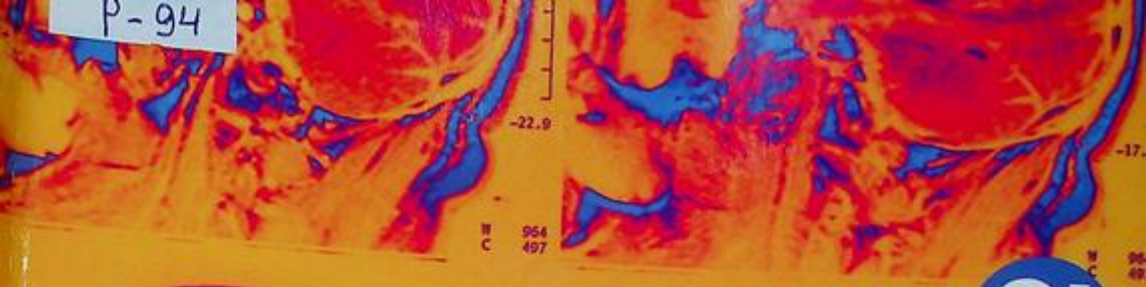
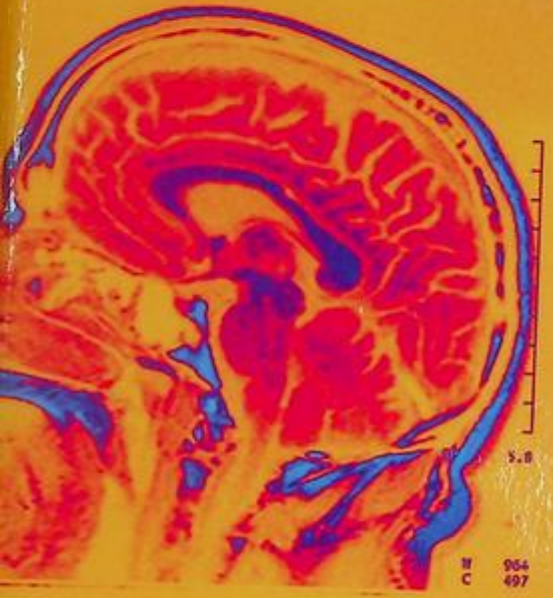


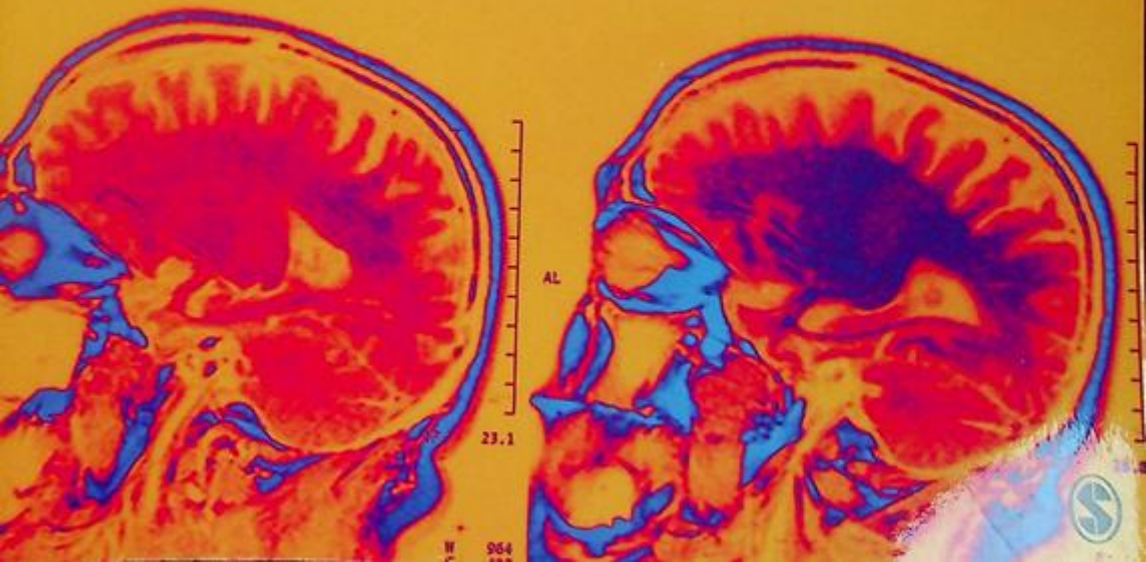
3 EDITION

# DRUGS AND THE NEUROSCIENCE OF BEHAVIOR

## An Introduction to Psychopharmacology

ADAM PRUS





# Drugs and the Neuroscience of Behavior

Third Edition

*To my psychopharm students*

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# Drugs and the Neuroscience of Behavior

## An Introduction to Psychopharmacology

**Third Edition**

№ 29394

**Adam Prus**

*Northern Michigan University*

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2455 Teller Road
Thousand Oaks, California 91320
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SAGE Publications Ltd.
1 Oliver's Yard
55 City Road
London EC1Y 1SP
United Kingdom

SAGE Publications India Pvt. Ltd.
B 1/I 1 Mohan Cooperative Industrial Area
Mathura Road, New Delhi 110 044
India

SAGE Publications Asia-Pacific Pte. Ltd.
18 Cross Street #10-10/11/12
China Square Central
Singapore 048423

Acquisitions Editor: Abbie Rickard
Editorial Assistant: Elizabeth Cruz
Content Development Editor: Emma Newsom
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Copy Editor: Laurie Pitman
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Proofreader: Liann Lech
Indexer: Integra
Cover Designer: Scott Van Atta
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Printed in Canada

*Library of Congress Cataloging-in-Publication Data*

Names: Prus, Adam J., author.

Title: Drugs and the neuroscience of behavior : an introduction to psychopharmacology / Adam Prus, Northern Michigan University.

Description: Third edition. | Los Angeles : SAGE Publishing, [2021] | Includes bibliographical references and index.

Identifiers: LCCN 2020010317 | ISBN 9781544362571 (paperback) | ISBN 9781544362588 (epub) | ISBN 9781544362595 (epub) | ISBN 9781544362601 (pdf)

Subjects: LCSH: Psychopharmacology. | Psychotropic drugs—Side effects.

Classification: LCC RM315 .P718 2021 | DDC 615.7/8—dc23
LC record available at https://lccn.loc.gov/2020010317

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FSC® C103567

20 21 22 23 24 10 9 8 7 6 5 4 3 2 1

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# Preface

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

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

## How the Materials Are Organized

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

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

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

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

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

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

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

## Changes in the Third Edition

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

Major new topics include coverage of:

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

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

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

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

## Ancillaries

SAGE Edge offers online resources for review, study, and support. Go to **edge.sagepub.com/prus3e**

### Student Resources

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

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

### *Instructor Resources*

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

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

# Acknowledgments

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

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

Perry W. Buffington, University of Georgia

Elizabeth Caldwell, University of New Hampshire

Natalie A. Ceballos, Texas State University, San Marcos

Catherine L. Franssen, Longwood University

Eric Jackson, University of New Mexico

Steven E. Meier, University of Idaho

Dennis K. Miller, University of Missouri

Brian C. Nolan, Missouri Valley College

John Rossi III, Florida Gulf Coast University

Mansi A. Shah, Temple University

Katherine M. Serafine, The University of Texas at El Paso

Students have been a great source for suggestions on items to cover and for identifying content in need of refining. I hesitate a bit in listing individuals who helped in this regard, since I risk forgetting discussions in classrooms or hallways that might have prompted me to write or change something that I otherwise may not have considered. With this caveat stated, I point out (in alphabetical order) Skylar Korf, Cayla Lynch, Nathan Schultz, Natalie Strand, Alexis Thierry, and Edward Tunison as raising very interesting points that

helped me in crafting some topics in this book. I also reached to close colleagues for candid advice and they include (also in alphabetical order) Todd Hillhouse, Alan Pehrson, and Joseph Porter. And finally, I especially wish to thank my wife Jennifer and my kids Kendell and Daniel, who tolerated the many hours I spent shut in our home office tapping away at a laptop.

To all: thank you!

# About the Author

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

CHAPTER 1

# Introduction to Psychopharmacology

## Chapter Outline

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

## Learning Objectives

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

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

## Psychopharmacology

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

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

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

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

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

**TABLE 1.1 Names Used to Describe Psychopharmacology**

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

## Why Read a Book on Psychopharmacology?

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

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

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

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

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

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

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

## What Is a Drug?

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

**Drug**
An administered substance that alters physiological functioning

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

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

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

**FIGURE 1.1 Examples of Substances Used**

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

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

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

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

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

## STOP & CHECK

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

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

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

## Psychoactive Drugs Are Described by Manner of Use

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

**Instrumental drug use**
Using a drug to address a specific purpose

**Psychotropic drug**
Drug used to treat a psychological disorder

**Recreational drug use**
Using a drug entirely to experience the drug's effects

**Drug misuse**
Recreationally using a drug that has accepted instrumental uses

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

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

## Generic, Brand, Chemical, and Street Names for Drugs

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

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

**Brand name (or trade name)**
A trademarked name a company provides for a drug

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

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

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

**Chemical name**
A name that details a drug's chemical structure

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

**TABLE 1.2 Examples of Street Names for Selected Drugs**

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

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

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

**Street name**
An alternative name applied to a recreational or abused substance

## Drug Effects Correspond With Doses

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

**Dose**
Ratio of the amount of drug per an organism's body weight

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.

**Dose-effect curve**
Depicts the magnitude of a drug effect by dose

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

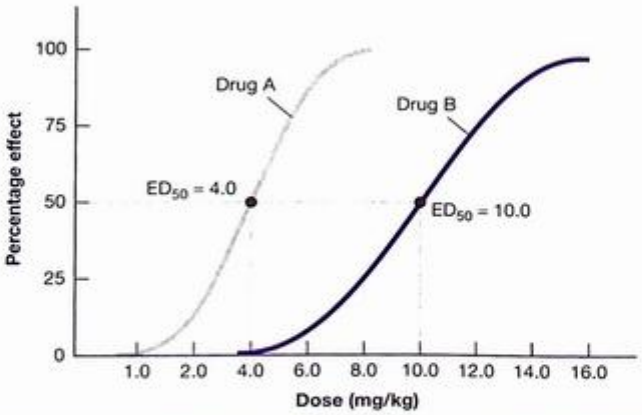
To describe the position of a dose-effect curve, researchers calculate an $ED_{50}$. An $ED_{50}$ is a value that represents the dose at which 50 percent of an effect was observed.[1] The "ED" stands for "effective dose."

**$ED_{50}$**
Value that represents the dose at which 50 percent of an effect was observed

As shown in Figure 1.2, drug A's $ED_{50}$ 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 $ED_{25}$ (i.e., dose at which 75 percent of the effect

**FIGURE 1.2 Dose-Effect Curves**

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




[1]Alternatively, an $ED_{50}$ value can reflect a dose at which 50 percent of the subjects exhibited a full effect.

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

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

**Potency**
Amount of drug used to produce a certain level of effect

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

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

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

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

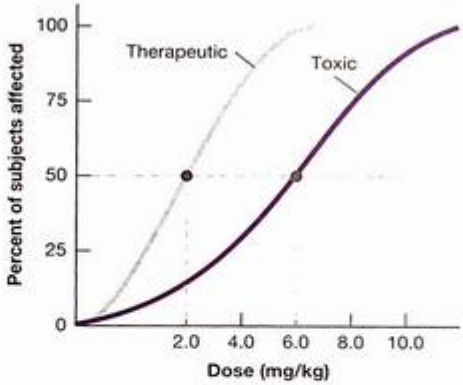
**Therapeutic index**
Ratio of a drug's toxic dose-effect curve value relative to therapeutic dose-effect curve value

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

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

**FIGURE 1.3 Therapeutic and Toxic Dose-Effect Curves**

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




**Certain Safety Index**
A therapeutic index calculated by dividing a $TD_1$ by an $ED_{99}$.

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

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

**Additive drug effects**
The magnitude of the combined drug effect is the sum of each drug's effect alone.

**Synergistic drug effects**
The magnitude of the combined drug effect is beyond the sum of each drug's effect alone.

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

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

## STOP & CHECK

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

1. The manner of usage. Individuals use therapeutic drugs instrumentally toward treating a disorder or ailment, whereas individuals take recreational drugs entirely to experience the drug's effects. 2. Therapeutic drugs are provided a generic name, which refers to the organizational fit of a drug with similar acting drugs, and a trade name, which is the company's brand name for the drug. 3. A dose is a ratio of the amount of drug per amount of body weight. Most of the instructions provided with over-the-counter drug packages advise taking pills based on an average adult weight. 4. A Certain Safety Index provides the safest approach for calculating a therapeutic index by dividing a toxic dose for 1 percent of subjects, referred to as a $TD_1$, by a 99 percent effective dose, referred to as an $ED_{99}$. When this calculation produces large therapeutic indexes, the toxic doses are much higher than therapeutically effective doses.

## Pharmacodynamics, Pharmacokinetics, and Pharmacogenetics

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

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

**Pharmacokinetics**
The physiological and biochemical actions of drugs.

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.

**Pharmacogenetics**
The study of how genetic differences influence a drug's pharmacokinetic and pharmacodynamic effects.

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

## Objective and Subjective Effects of Psychoactive Drugs

**Objective effects**
Pharmacological effects that can be directly observed by others

**Subjective effects**
Pharmacological effects that cannot be directly observed by others

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

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

**FIGURE 1.4** **Objective and Subjective Drug Effects**

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

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# BOX 1.1

## INSTRUMENTS USED FOR STUDYING SUBJECTIVE EFFECTS IN HUMANS

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

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

**BOX 1.1 FIGURE 1** **Sample From the Abbreviated Profile of Mood States Questionnaire**

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

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

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

*(Continued)*

(Continued)

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

For studies involving recreational substances, researchers often assess how much participants enjoy the effects of a drug. To do this, many studies use a *"liking" scale*, asking participants to rate, from strongly disliking to strongly liking, the effects felt from a substance administered to them by the researchers (in a safe, controlled laboratory setting). These scales may have labels drawn on a horizontal line, allowing a study volunteer to mark the degree of liking for a drug's effects on the line. For this approach, we refer to these instruments as having *visual analog scales*. For example, Soria and colleagues (1996) used visual analogy scales to assess the subjective effects of nicotine in smokers and nonsmokers. Smokers, on average, placed marks around 50mm for lines that ran from 0mm to 100mm to rate nicotine's "good effects." Nonsmokers, on the other hand, placed marks around 15mm.

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

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

## STOP & CHECK

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

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

## Study Designs and the Assessment of Psychoactive Drugs

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

**Dependent variable**
A study variable measured by a researcher

**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.

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

### Experiments

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

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

**TABLE 1.3 Correlational and Experimental Studies**

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

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

**Placebo**
Substance identical in appearance to a drug but physiologically inert

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.

**Single-blind procedure**
When researchers do not inform study participants which treatment or placebo they received

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.

**Double-blind procedure**
When neither participants nor investigators know the treatment assignments during a study

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.

**Open-label studies**
Assignment of study treatments without using blinded procedures

## Correlational Studies

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

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

identifies one of the variables as an independent variable[2], but the conditions of this variable are not altered like they are for an experiment. For example, to study the effects of long-term MDMA use on memory, a researcher might recruit participants who used MDMA and then measure each participant's ability to recall words from a list. We could use the duration of MDMA use as the *independent variable*, and each participant's level of memory serves as the *dependent variable*. The investigators did not alter the independent variable, but instead studied duration of MDMA use and memory ability as conditions that already existed. Researchers might infer a relationship between MDMA use and memory if long-term MDMA users exhibited poor word recall and if infrequent MDMA users exhibited good word recall. But, it is important that correlational studies do not indicate that a variable *causes* changes to another variable.

## Validity and the Interpretation of Study Findings

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

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

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**TABLE 1.4 Types of Validity**

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

[2]Alternatively, correlational studies can use the term *predictor* instead of *independent*

საჯარო სამართლის იურიდიული პირი
ბათუმის შოთა რუსთაველის
სახელმწიფო უნივერსიტეტის
ბიბლიოთეკა
№

**Internal validity**
Control of variables with potential to influence a dependent variable

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

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

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

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

**External validity**
Refers to how well study findings generalize beyond the study conditions

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

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

**Teratogen**
Substance harmful to a fetus

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

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

**Face validity**
Appearance of a test measuring what a researcher considers it to measure

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

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

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

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

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

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

**Predictive validity**
How well a model predicts treatment effects

## STOP & CHECK

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

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

## Ethical Considerations in Research

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

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

### A Lack of Feasible Alternatives to Animals

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

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

### High Predictive Value for Drug Effects in Humans

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

## The Regulation of Animal Research

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

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

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

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

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

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

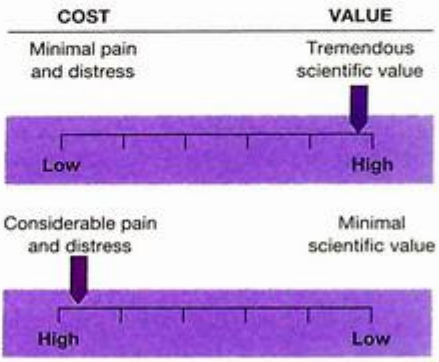
IACUCs also weigh the proposed study's ethical costs. **Ethical cost** assessments weigh the value of potential research discoveries against the potential pain and distress experienced by research subjects (**Figure 1.5**). For example, IACUC members easily justify painless experiments in animals that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

**The 3 Rs**
A review process for animal research that considers "replacement," "reduction," and "refinement" to determine the necessity of using animals, minimum number of animals needed, and procedures to minimize pain and distress

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

**FIGURE 1.5 Ethical Costs for Animal Research**

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




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

## Researchers Consider Many Ethical Issues When Conducting Human Research

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

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

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 may range from fines to freezing an institution's federal research funding.

## STOP & CHECK

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

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

## From Actions to Effects: Therapeutic Drug Development

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

Pharmaceutical drug research and development generally occurs in several stages (Blake et al., 2006; 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**

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

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

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

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

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

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

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

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

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

**Safety pharmacology**
The study of a drug's adverse effects.

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

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

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

**Treatment arms**
Number of treatments and doses provided to patients described in a clinical study.

**Clinical study reports**
Detailed summaries of a clinical study's design and results.

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

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

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

**TABLE 1.6 Clinical Trial Phases**

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

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

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

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

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

## STOP & CHECK

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

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

## 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 much of the U.S. population, and antidepressant medications are used by close to a third of the Western population. Learning about psychopharmacology provides a greater understanding of behavior and how mental disorders are treated. Defined as substances that alter physiological functioning, drugs are known by generic, brand, chemical, and street names. Drug amounts used are described as doses, and understanding drug effects and actions requires knowledge of pharmacokinetic and pharmacodynamic actions. Moreover, genetic differences account for varying drug effects among individuals. Drugs fall into two categories: therapeutic drugs and recreational drugs. However, many drugs cross both categories, depending on their usage. Researchers study the objective and subjective effects of drugs in studies that address the importance of drawing valid inferences from study results. Drug studies often employ either animal or human subjects, in 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
Drug 4
Instrumental drug use 5
Psychotropic drug 5
Recreational drug use 6

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

## Neurons

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

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

**FIGURE 2.1 Soma of a Neuron**

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

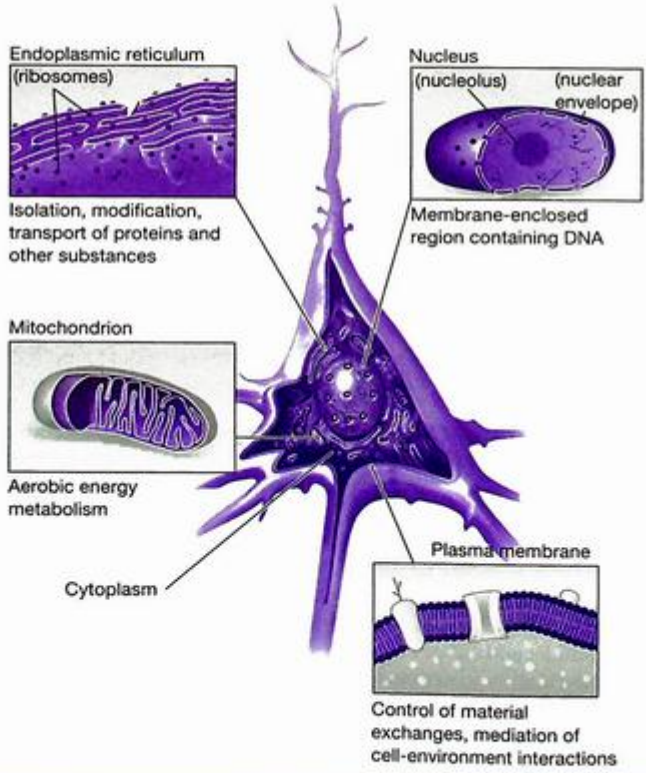
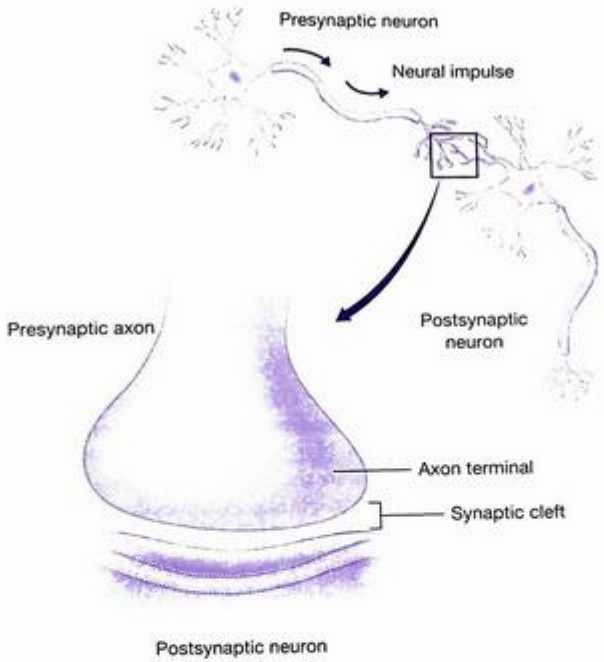


**FIGURE 2.2 Major Components of a Neuron**

The four major components of a neuron are the soma, dendrites, an axon, and an axon terminal. Dendrites receive information, and axons send information.




Generally, a neuron has many dendrites that branch off from the soma. The **dendrites** of a neuron receive information from other neurons. Small stems called *dendritic spines* grow along the length of dendritic branches. The membranes of dendrites and dendritic spines contain proteins called *receptors* that neurotransmitters can activate. When activated, receptors cause changes in the functioning of the neuron.

**Dendrites**
Parts of a neuron that receive information from other neurons

**Axons** release neurotransmitters for signalling with other neurons. Most neurons have only one axon, which branches from the soma, usually opposite from the dendrites. An axon begins at a part of the soma called the *axon hillock* and ends with multiple branches containing axon terminals.[1] These branches are called *axon collaterals*. An axon terminal contains and releases neurotransmitters near a part of a dendrite called a *postsynaptic terminal*. The postsynaptic terminal contains

**Axons**
Part of a neuron that releases neurotransmitters for signalling with other neurons

[1]Also referred to as *presynaptic terminals*.

receptors for neurotransmitters. The small space between the axon terminal and postsynaptic terminal is called the *synaptic cleft*. The term **synapse** refers to the components that comprise this connection—the axon terminal, the postsynaptic terminal, and the synaptic cleft.

**Synapse**
Components that make up a connection between neurons that includes an axon terminal, postsynaptic terminal, and synaptic cleft

Neuroscientists use different terms to describe the location of a neuron and the direction of its axon. The term **interneuron** describes a neuron with the soma and axon found within the same structure (**Figure 2.3**). An *afferent* neuron has an axon *going to* another structure. **Sensory neurons**, which convey sensory information via axons to the central nervous system, are considered afferent neurons. An *efferent* neuron has an axon *coming from* a structure. **Motor neurons** (or **motoneurons**), which convey motor information via axons from the central nervous system, are considered efferent neurons (Figure 2.3). Thus, the terms *afferent* and *efferent* can refer to any structure being studied. For example, the thalamus, a structure that routes sensory information to different parts of the cerebral cortex, has both types of neurons: afferent neurons send axons *to* the thalamus, and efferent neurons send axons *from* the thalamus.

**Interneuron**
Neuron with the soma and axon found within the same structure

**Sensory neuron**
Neuron that conveys sensory information via axons to the central nervous system

**Motor neuron (or motoneuron)**
Neuron that conveys motor information via axons from the central nervous system

## Glial Cells

Glial cells consist of three different types: (1) oligodendrocytes, (2) astrocytes, and (3) microglial cells (**Figure 2.4**). **Oligodendrocytes** extend their membranes around axons to form a material called *myelin*. Myelin is found in segments along the length of an axon, and myelin serves to facilitate the movement of electrical impulses down an axon (more on this in Chapter 3). A single oligodendrocyte can provide myelin for multiple neurons and for multiple segments of an axon. *Schwann cells* are like oligodendrocytes, but they are found in the peripheral nervous system and they extend themselves around an axon to form only a single segment of myelin. Motor dysregulation, paralysis, and other symptoms of multiple sclerosis result from degeneration of myelin sheaths surrounding axons in the nervous system.

**Oligodendrocyte**
Glial cell that forms a material called myelin around the axons of neurons

**Astrocytes** play a role in forming the blood–brain barrier, facilitating neuronal function, and responding to injury. Astrocytes form the blood–brain barrier (discussed in Chapter 5) by forcing endothelial cells to fit tightly together. Astrocytes support neuronal function through acting at synapses during neurotransmission, which we consider in Chapter 3.

**Astrocyte**
Glial cell that plays a role in forming the blood–brain barrier, facilitating neuronal function, and responding to injury

**Microglial cells** remove normal cellular waste and serve as immune cells in the central nervous system. Two types of microglial cells exist: M1 and M2. M1 microglial cells release chemicals that promote inflammation and can damage the blood–brain barrier, whereas M2 microglial cells release chemicals that reduce inflammation and promote the growth and development of cells. Inflammation caused by M1 microglial weakens the blood–brain barrier, allowing in cells that can damage neurons. The potential for inflammation-induced damage to neurons to contribute to mental and neurological disorders provides an important reason to study microglial cells (Nakagawa & Chiba, 2015).

**Microglial cell**
Glial cell that removes normal cellular waste and serves as an immune cell in the central nervous system

**FIGURE 2.3** **Motor Neurons, Sensory Neurons, and Interneurons**

Motor neurons convey movement information to muscles in the body, and sensory neurons convey sensory information to the central nervous system (CNS). Relative to the central nervous system, motor neurons are efferent neurons (going away from the CNS), and sensory neurons are afferent neurons (going to the CNS). Interneurons have the soma, dendrites, and axon all contained within the same structure.

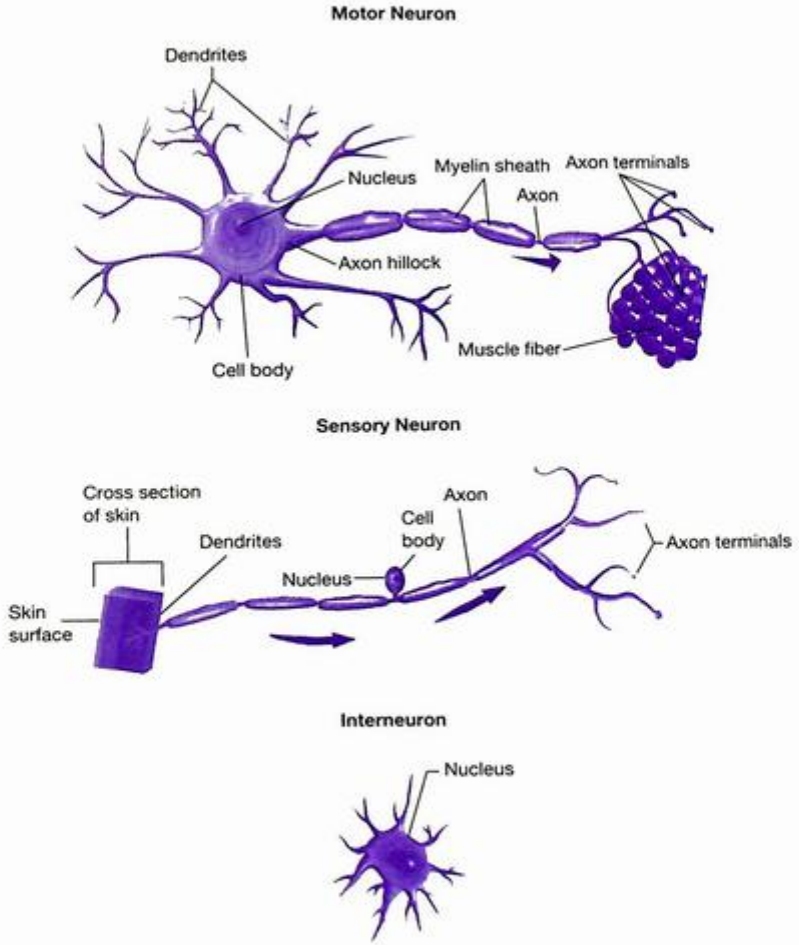
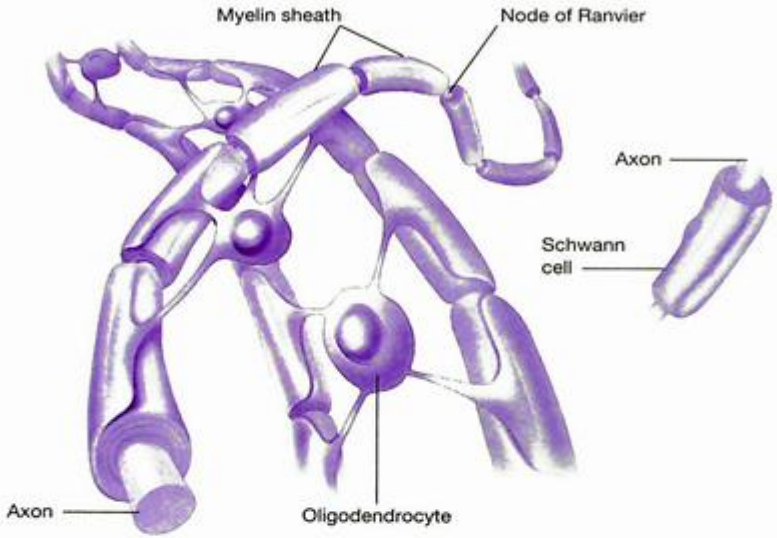


**FIGURE 2.1 Glial Cells**

Glial cells support neuronal functioning. Oligodendrocytes and Schwann cells provide myelin sheathing for axons. Astrocytes form the blood–brain barrier, break down certain neurotransmitters, and respond to injury in the nervous system. Microglial cells remove cellular waste.




## STOP & CHECK

1. What are the two types of cells found in the brain?
2. _____ receive information from other neurons, and _____ send information to other axons.
3. Sensory neurons are also called _____ neurons because axons go to the central nervous system.
4. Which types of glial cells provide myelin sheathing for axons?

1. Neurons and glial cells 2. Dendrites, axons 3. afferent 4. Oligodendrocytes produce myelin sheathing around axons in the central nervous system, and Schwann cells produce myelin sheathing around axons outside of the central nervous system.

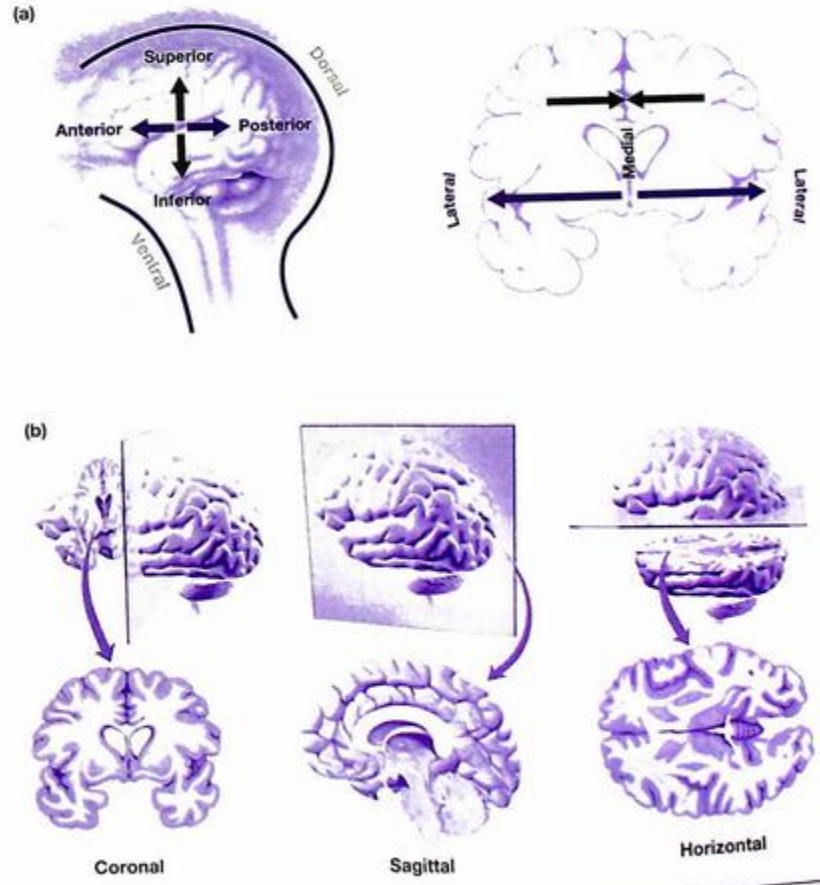
## The Nervous System

Learning the basic terms used to describe where nervous system structures are located is an important first step for studying the brain. Standard terms describe

the location of structures in the nervous system. For example, we refer to the front portion of the brain as *anterior* and the back portion of the brain as *posterior*. The bottom of the brain, the side that faces toward the stomach, is referred to as the *ventral* side, and the top of the brain is referred to as the *dorsal* side. We refer to structures near the sides of the brain as *lateral*; structures near the middle of the brain are described as *medial*. **Figure 2.5** presents these and other terms that describe structures in the brain.

**FIGURE 2.5** **The Human Brain**

The human brain can be dissected in coronal (i.e., frontal), sagittal, and horizontal sections. We use special terms to describe the location of structures in the brain. See text for further details.



Looking at structures inside the brain may be accomplished through any of three basic types of dissection planes. Slicing the brain from anterior to posterior produces a *coronal* (or *frontal*) section. We produce horizontal sections by slicing the brain from dorsal to ventral, and sagittal sections provide lateral views of the brain. Dissection planes provide different perspectives of a structure.

## The Peripheral Nervous System

The nervous system consists of two systems: (1) the peripheral nervous system and (2) the central nervous system (CNS). Much of what we discuss in this book pertains to the central nervous system, which consists of the brain and spinal cord. Drugs also have many effects on the peripheral nervous system, which contains two subsystems called the *somatic nervous system* and *autonomic nervous system* (**Figure 2.6**).

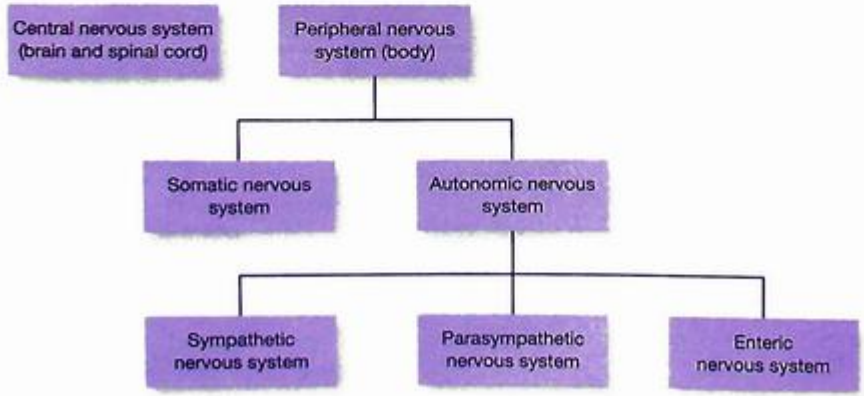
**Somatic nervous system**
System responsible for delivering voluntary motor signals from the central nervous system to muscles throughout the body and for conveying sensory information from the body to the central nervous system

### *The Somatic Nervous System: Delivering Motor Signals to Muscles and Sensory Signals to the Spinal Cord*

The **somatic nervous system** is responsible for delivering voluntary motor signals from the CNS to muscles and for conveying sensory information from the body to the CNS. Thus, the somatic nervous system is made up of motor neurons and sensory neurons. Sensory neurons send information to the dorsal part of the spinal cord (through the *dorsal root* to the *dorsal horn*), whereas motor signals are sent

**FIGURE 2.6** The Peripheral Nervous System

The peripheral nervous system contains the somatic nervous system and the autonomic nervous system. The autonomic nervous system consists of the sympathetic nervous system, the parasympathetic nervous system, and the enteric nervous system.



to muscles from the ventral part of the spinal cord (from the *ventral horn* to the *ventral root*) (**Figure 2.7**). The point where a motor neuron meets a muscle fiber is called the *neuromuscular junction*. Muscles contract when motor neurons release the neurotransmitter acetylcholine at neuromuscular junctions.

**Autonomic nervous system** System that controls involuntary movements for vital functions, such as heartbeat, breathing, swallowing, and digestion

**Sympathetic nervous system** Subsystem of the autonomic nervous system that prepares the body for rigorous activity by increasing heartbeat, inhibiting digestion, and opening airways, among many other involuntary functions

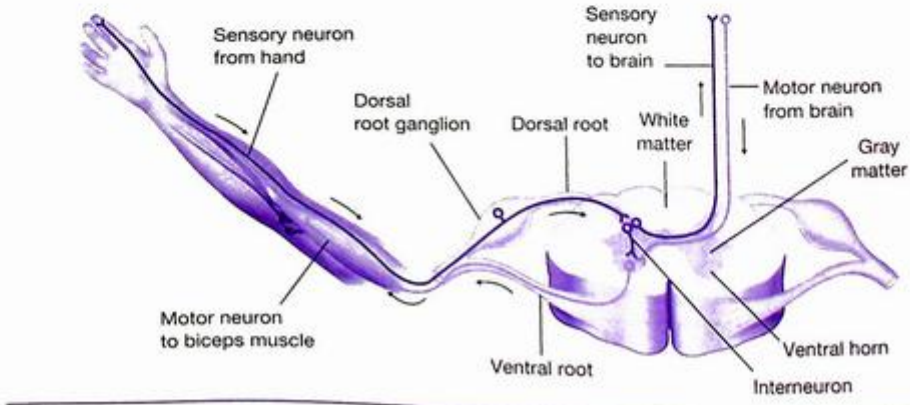
### *The Autonomic Nervous System: Controlling Vital Functions*

Whereas the somatic nervous system produces voluntary movement, the **autonomic nervous system** controls involuntary movements for functions such as heartbeat, breathing, swallowing, digestion, and sweating by controlling heart muscle, smooth muscle, and exocrine glands. Exocrine glands secrete substances through a duct, such as sweat, saliva, and tears. The autonomic nervous system consists of three systems: (1) the sympathetic nervous system, (2) the parasympathetic nervous system, and (3) the enteric nervous system (**Figure 2.8**). The **sympathetic nervous system** prepares the body for rigorous activity by increasing heartbeat, inhibiting digestion, and opening airways, among many other involuntary functions. The **parasympathetic nervous system** is dominant during relaxed states and decreases heartbeat, stimulates digestion, and closes airways. The **enteric nervous system** controls digestion via communication within its system and with the central nervous system (Furness, 2007).

Both the sympathetic and parasympathetic nervous systems contain ganglia (singular *ganglion*). *Ganglia* are clusters of neuron cell bodies for neurons in the sympathetic and parasympathetic nervous systems. A ganglion fully contains a

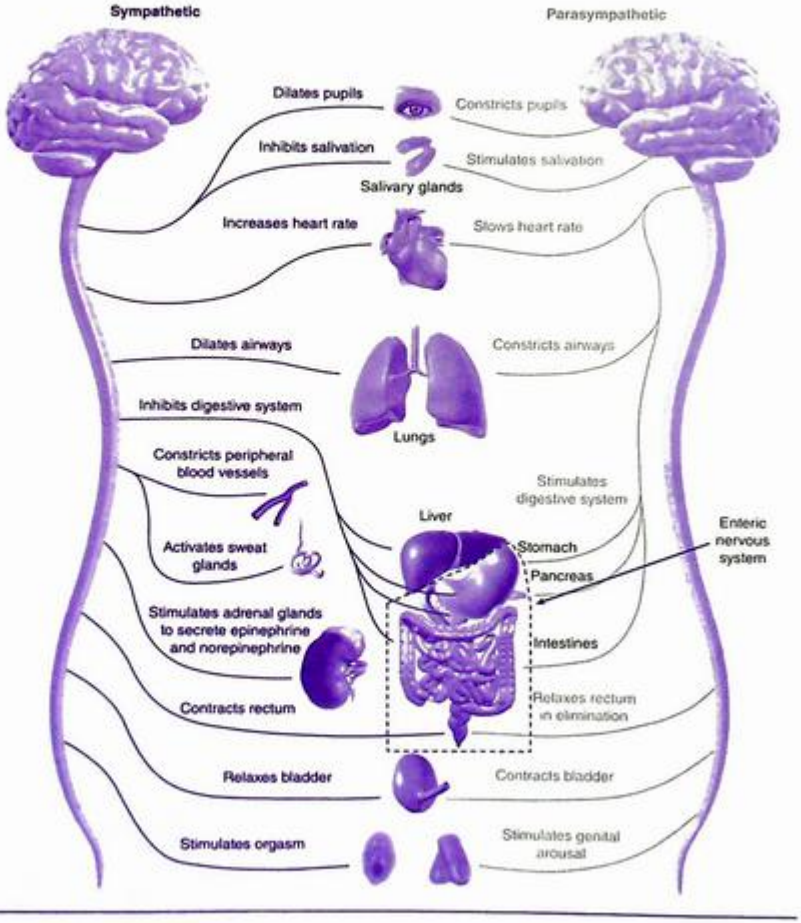
**FIGURE 2.7 Spinal Cord**

Sensory neurons send information to the dorsal part of the spinal cord, whereas motor signals are sent to muscles from the ventral part of the spinal cord. Gray matter appears in the middle portion of the spinal cord forming an H shape. White matter appears in the outermost portions of the spinal cord.



## FIGURE 2.8 Autonomic Nervous System

The autonomic nervous system is made up of the sympathetic nervous system, the parasympathetic nervous system, and the enteric nervous system. The sympathetic nervous system enhances the activity of organs in the body and the parasympathetic nervous system diminishes the activity of these same organs. The activation of each system occurs by preganglionic neurons releasing acetylcholine in ganglia, which binds to receptors on postganglionic neurons. The enteric nervous system controls digestion, and it carries out independent functions as well as responding to information from the central nervous system.



neuron's soma and dendrite, while a neuron's axon extends from the ganglion to a muscle or gland. We call this a *postganglionic* neuron because its axon comes after the ganglion and goes to a muscle or gland. A neuron that instead sends an axon from the spinal cord to a ganglion is referred to as a *preganglionic* neuron.

**Parasympathetic nervous system** Subsystem of the autonomic system that is dominant during relaxed states, including decreases in heart rate, stimulation of digestion, and the closing of airways

Preganglionic neurons control sympathetic and parasympathetic nervous system neurons by releasing the neurotransmitter acetylcholine at synapses for postganglionic neurons. Through the process of neurotransmission (discussed in Chapter 3) acetylcholine makes these postganglionic neurons more active. Axons for the activated postganglionic neurons then release neurotransmitters at their axon terminals. This leads target muscles or glands to have increased (for sympathetic nervous system neurons) or decreased (for parasympathetic nervous system neurons) activity.

**Enteric nervous system** Subsystem of the autonomic system that controls digestion via communication within its system and with the central nervous system

The enteric nervous system consists of 200-600 million neurons found within the gastrointestinal tract, with thousands of ganglia located throughout the system. While this system communicates with the central nervous system, the enteric nervous system handles many of its functions independently—this makes the system unique from the other systems in the peripheral nervous system. As discussed in Chapter 3, the nature of afferent communication to the central nervous system creates a number of intriguing research questions concerning bacteria that live in the gut and the chemical messengers released from these bacteria (Furness, 2007).

## STOP & CHECK

1. Brain sections produced by slicing the brain from anterior to posterior are referred to as _____ sections.
2. The somatic nervous system delivers movement signals to muscles by releasing acetylcholine at _____.
3. The _____ system controls vital functions such as breathing and heartbeat.

1. coronal 2. neuromuscular junctions 3. autonomic

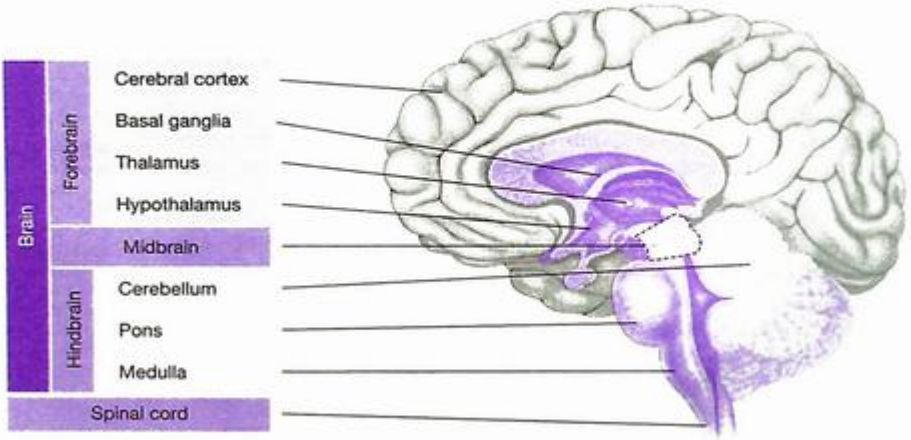
## The Central Nervous System

The brain and spinal cord make up the central nervous system (**Figure 2.9**). The surface of the brain—the **cerebral cortex**—has hills called *gyri* (singular *gyrus*) and valleys called *sulci* (singular *sulcus*). The base of the brain, where the spinal cord meets, is called the *brain stem*. Above the brain stem sits a structure called the *cerebellum*. The brain is divided into two hemispheres, left and right. Structures found in one hemisphere have a matching structure in the other hemisphere.

**Cerebral cortex** The surface of the brain, comprising gyri and sulci

**FIGURE 2.9 Regions of the Brain**

The brain is divided into three different divisions or regions called the *hindbrain*, *midbrain*, and *forebrain*.




The brain has three different divisions called the *hindbrain*, *midbrain*, and *forebrain*, also shown in Figure 2.9. The hindbrain consists mostly of the brain stem, and it begins where the spinal cord meets the brain stem at a structure called the *medulla*. The midbrain comprises a region between the hindbrain and forebrain; it includes the *inferior colliculus*, which plays a role in auditory processing, and the *superior colliculus*, which directs eye movement. The forebrain includes the rest of the brain and contains the cerebral cortex and structures beneath the cerebral cortex, such as the *corpus callosum*, *basal ganglia*, *thalamus*, and *hypothalamus*.

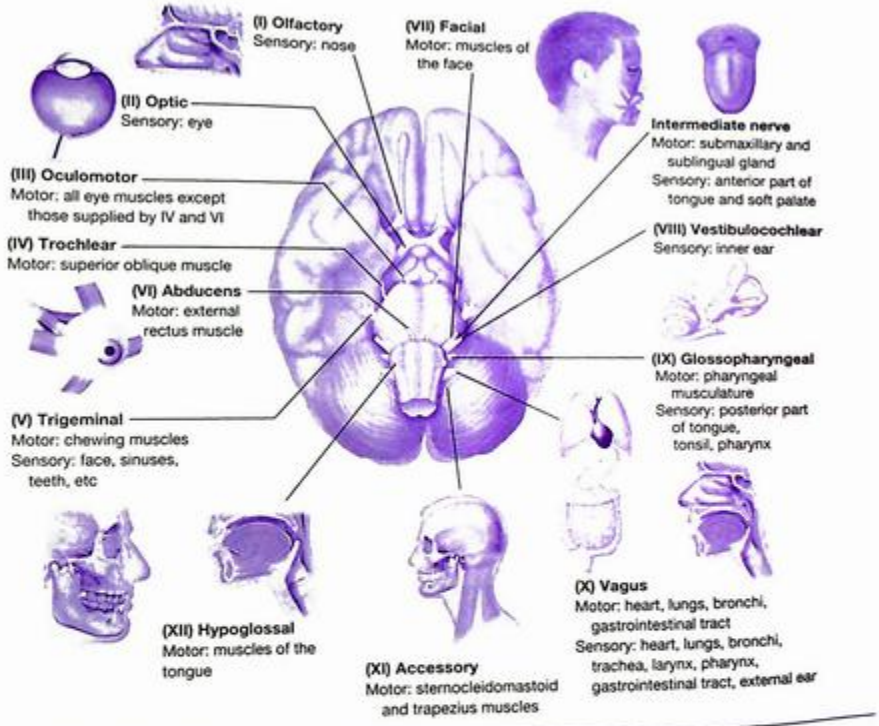
### *The Medulla and Hypothalamus: Controlling Unlearned Behaviors*

**Medulla**
Structure that controls the autonomic nervous system and is situated where the spinal cord meets the hindbrain

We previously discussed the autonomic system, which maintains vital functions in the body. The autonomic nervous system is controlled by the medulla (**Figure 2.10**). As already described, the **medulla** rests where the spinal cord meets the hindbrain. In fact, from the surface, the medulla looks like a thicker section of spinal cord. Through controlling the autonomic nervous system, the medulla controls basic autonomic functions such as breathing, heart rate, and vomiting. Many of the cranial nerves also come from the medulla. These nerves are devoted to movement and sensations of the head (**Figure 2.10**). There are 12 cranial nerves, each noted by its number and name.

**FIGURE 2.10** **Ventral Surface of the Brain**

The ventral side of the brain reveals many features, including the structures in the brain stem and all 12 of the cranial nerves.




Source: Encyclopaedia Britannica/Contributor/Universal Images Group/Getty.

The vagus nerve (roman numeral X) differs from the functions of the other cranial nerves because it controls and receives sensory information from various internal organs in the body, including the heart, liver, and intestines. The vagus nerve serves as a primary line of intercommunication between the enteric nervous system and the central nervous system. Mostly afferent axons (again, going to the central nervous system) make up the vagus nerve, and in the brain, the vagus nerve sends input to a hindbrain structure called the *nucleus of the solitary tract*. Outputs from the nucleus of the solitary tract reach the medulla (in the hindbrain) and many structures in the forebrain, including the hypothalamus, thalamus, amygdala, and cerebral cortex (Schachter & Saper, 1998).

Given that the vagus nerve is accessible outside of the brain and that it interacts with numerous systems in the brain, clinical researchers have explored *vagal nerve stimulation* as a therapeutic strategy. Vagal nerve stimulation occurs through surgically installing an electrical pulse generator in the chest and connecting it to wire wrapped around a portion of the vagus nerve in the throat. The procedure is FDA approved in the United States for reducing seizures in epilepsy and for treatment-resistant depression (i.e., depression not improved by psychotherapy or antidepressant drugs) (O'Reardon, Cristancho, & Peshek, 2006; Schachter & Saper, 1998).

Damaging the medulla can be life threatening, and suppressing its functioning can be just as dangerous. Narcotics and central nervous system depressants suppress medullary functions, which can be fatal at high-enough doses. Moreover, mixing two or more CNS depressants at otherwise safe amounts can produce combined suppressant effects on medullary functions.

**Hypothalamus**
Structure found in the forebrain that maintains important physiological conditions, in part by motivating an organism's behavior

The **hypothalamus**, a structure found in the forebrain, maintains important physiological conditions (**Figure 2.11**). The hypothalamus maintains many physiological processes by motivating an organism's behavior. When the body requires food, for example, the hypothalamus elicits feelings of hunger. Similarly, the hypothalamus elicits thirst when we become dehydrated. Other processes the hypothalamus regulates include body temperature, sleep, and motivation for sexual activity.

The hypothalamus controls the *pituitary gland*, which sits on the ventral surface of the brain. The pituitary gland releases many hormones into the bloodstream, affecting organ functions in the body. These effects include water absorption into the kidneys, growth, thyroid function, and reproductive functions. The hypothalamus also controls the *pineal gland*, another forebrain structure that is responsible for the release of *melatonin*, a sleep-regulating hormone.

## STOP & CHECK

1. The central nervous system contains the brain and _____.
2. What is the primary structure in the brain for controlling autonomic functions?
3. How does the hypothalamus alter hormone levels in the body?

1. spinal cord 2. The medulla 3. The hypothalamus controls the pituitary gland, which releases many hormones throughout the body.

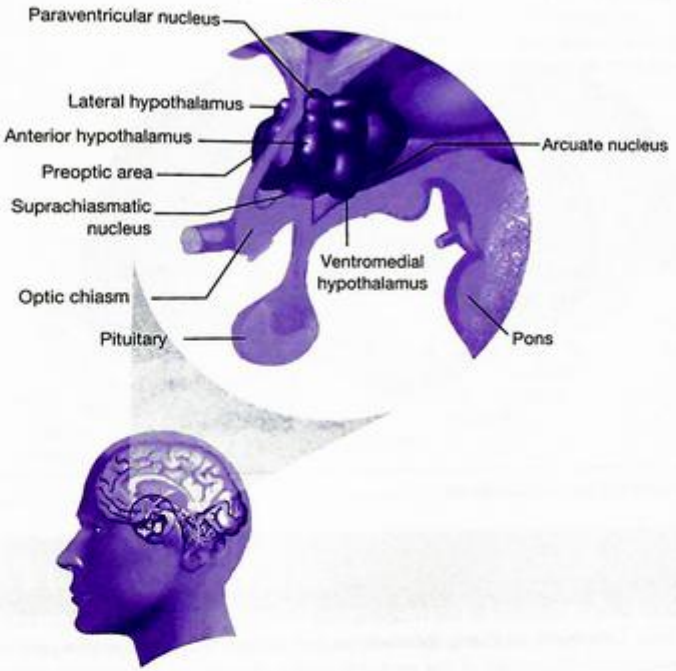
**Limbic system**
Series of structures that together appear to form a ring around the thalamus and hypothalamus

### *The Limbic System: Controlling Emotional Behaviors*

The **limbic system** consists of a series of structures that together form a ring around the thalamus and hypothalamus. These limbic system structures include the *cingulate gyrus*, *hippocampus*, *amygdala*, and *olfactory bulb* (**Figure 2.12**). Many structures within the limbic system control emotional behavior. The amygdala, for

**FIGURE 2.11 The Hypothalamus**

The hypothalamus plays an important role in homeostasis, partly by eliciting motivation for various physiological activities such as eating and drinking.




example, facilitates fear and aggression. Many drugs that reduce anxiety decrease the activity of neurons in the amygdala.

The **nucleus accumbens** rests adjacent and anterior to the amygdala and facilitates rewarding effects. For this reason, we refer to the nucleus accumbens as the brain's *reward center*. The nucleus accumbens belongs to a network of other structures referred to as the *reward circuit*. Chapter 5 presents more information on the brain's reward circuitry and the role this circuitry plays in the rewarding effects of abused substances.

**Nucleus accumbens** Limbic system structure that facilitates rewarding effects

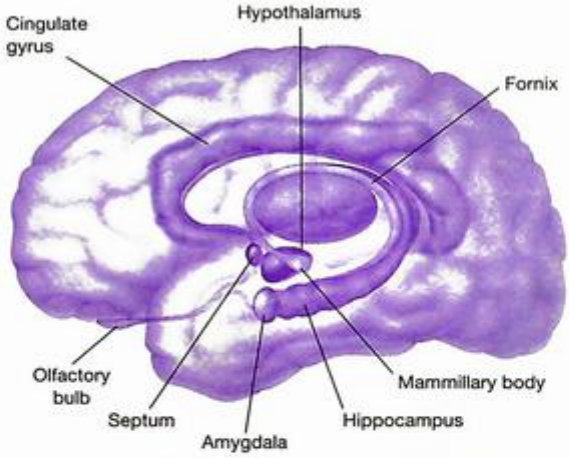
### *The Cerebral Cortex: Processing Sensory Information, Controlling Cognitive Functions, and Eliciting Movement*

Four lobes divide the cerebral cortex (**Figure 2.13**). The **occipital lobe** is the most posterior portion of the cerebral cortex and processes visual information. The

**Occipital lobe** Region of the cerebral cortex important for processing visual information

**FIGURE 2.12 The Limbic System**

The limbic system generally is important for emotion, although the hippocampus also plays an important role in long-term memory.




*Source:* Carolina Hrejsa/Body Scientific Intl.

**Temporal lobe** Region of the cerebral cortex important for processing auditory information and supporting language comprehension and production

**Parietal lobe** Region of the cerebral cortex important for processing touch information

**Frontal lobe** Region of the cerebral cortex important for decision making and movement

**Prefrontal cortex** Most anterior part of the frontal cortex; an integration area for all types of sensory input; initiates movements

**Thalamus** Forebrain structure that routes sensory information from the body to the appropriate lobes

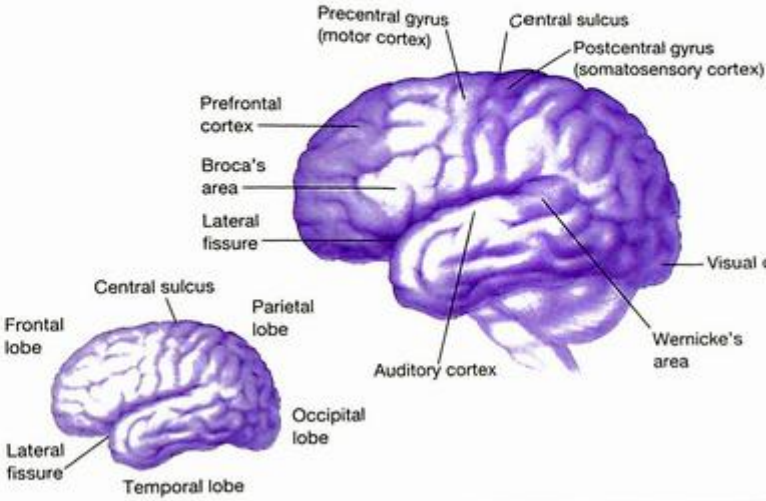
**temporal lobe** is anterior to the occipital lobe and below the parietal lobe. The temporal lobe processes auditory information and supports language comprehension and production. This area of the cerebral cortex also processes certain aspects of vision, including shape and color analysis. The **parietal lobe** is anterior to the occipital lobe and above the temporal lobe and includes the *somatosensory cortex*, the structure responsible for processing touch information from the body. The parietal lobe also analyzes visual information that contains movement.

The **frontal lobe**, which is at the anterior of the brain, supports decision making and movement. The frontal lobe contains the motor cortex. The most anterior part of the frontal lobe is called the **prefrontal cortex** and is an integration area for all types of sensory input and where the signal to produce movement occurs. Prefrontal cortical function also supports short-term memory and attention.

The **thalamus** routes sensory information from the body to the appropriate lobes. For example, visual information is sent from the eyes through the thalamus and to the occipital lobe, whereas auditory information is sent from the ears through the thalamus and to the temporal lobe. Olfactory information, however, is sent directly to the prefrontal cortex. After processing, all sensory information integrates in the prefrontal cortex.

**FIGURE 2.13 Lobes of the Cerebral Cortex**

Each lobe of the cerebral cortex processes different types of sensory information. The prefrontal cortex, wit
lobe, is an integration center for all types of sensory information.




## STOP & CHECK

1. What are the primary functions of the amygdala and nucleus accumbens?
2. Which lobe analyzes sound, including language?
3. What role does the thalamus play in processing sensory information?

1. The amygdala elicits feelings of fear, anxiety, and aggression, whereas the nucleus accumbens elicits rewarding effects. 2. Temporal lobe 3. The thalamus routes sensory information to the appropriate lobes of the cerebral cortex.

### *The Frontal Lobe and Basal Ganglia: Controlling Voluntary Movement*

After the prefrontal cortex signals a movement to occur, the **motor cortex** sends movement signals to the body via neurons (in this case, referred to as *tracts*) that cross from one hemisphere to the opposite side of the body to the limbs, hands, and feet. Tracts sent to the middle parts of the body, for posture and balance, have far fewer neurons crossing to the opposite side of the body.

**Basal ganglia**
Forebrain structure that aids in the stabilization of movement

The **basal ganglia** act to stabilize voluntary movements (**Figure 2.14**). The basal ganglia, also called the *striatum*, have three major substructures: the *caudate nucleus*, the *putamen*, and the *globus pallidus*. The term *ganglia* used for this structure comes from early anatomical studies that considered these to be distinct structures, but modern physiologists consider the basal ganglia as a single structure (Lanciego, Luquin, & Obeso, 2012). The *substantia nigra* aids in regulating activity in the basal ganglia. The primary symptoms of Parkinson's disease, a disorder characterized by muscle rigidity, tremor, and resistance to voluntary movement, occurs from the destruction of substantia nigra neurons that go to the basal ganglia. Many of the first drugs to treat schizophrenia, called *antipsychotic drugs*, disrupt these neurons, leading to Parkinson-like symptoms called *extrapyramidal side effects*.

**Pons**
A hindbrain structure that elicits startle reflexes

**Cerebellum**
A hindbrain structure that facilitates balance and the timing of movements

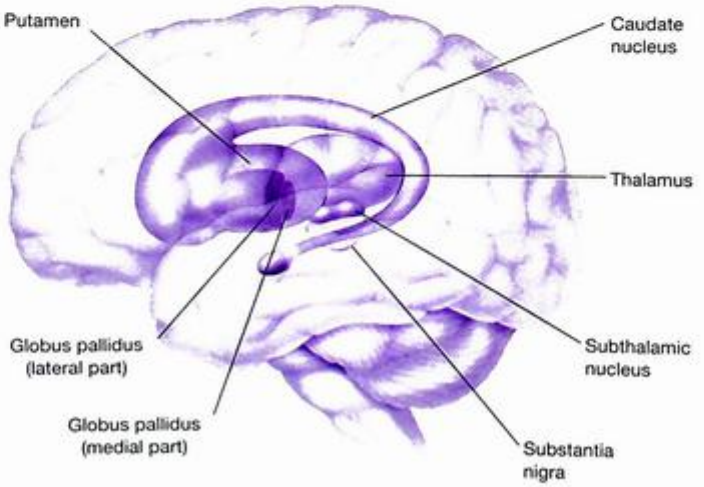
Some other components of the overall motor system must be noted. The **pons**, a structure located just above the medulla in the hindbrain, elicits startle reflexes. The **cerebellum** facilitates balance and the timing of movements.

### *Learning and Memory Processes in the Brain*

Psychologists characterize short- and long-term memories in different ways. Most consider short-term memory as working memory. *Working memory* consists of short-term verbal or nonverbal memories employed when carrying out a task. In essence, we are "working" with memory. *Long-term memory* (or *reference memory*),

**FIGURE 2.11 Basal Ganglia**

The basal ganglia, which include the globus pallidus, putamen, and caudate nucleus, regulate movement signals sent from the motor cortex.



consists of stored verbal and nonverbal information. Long-term memories include information that we can declare, such as the capital of the United States, or information we can demonstrate, such as how to swing a golf club.

The prefrontal cortex facilitates working memory function. Recall that information from all sensory modalities integrates in the prefrontal cortex. The prefrontal cortex uses this information to control behavior when engaging in a task.

Long-term memory formation and retrieval requires the **hippocampus**. The hippocampus then sends information to the prefrontal cortex, possibly for use during working memory function. Damage to the hippocampus in Alzheimer's disease may account for impairments in long-term memory. Long-term motor memories, also referred to as *procedural memories*, may depend on the basal ganglia. Procedural memories include such things as riding a bicycle or tying a shoelace.

**Hippocampus**
A forebrain structure in the limbic system important for long-term memory

Other parts of the brain indirectly aid memory formation by keeping the brain active. Many of these parts are found in the **reticular activating system**, which includes the *reticular formation, tegmentum, thalamus*, and *hypothalamus*. The activity within these structures ultimately supports arousal in the cerebral cortex. Another structure important for cortical arousal is the basal forebrain area. Drugs that increase cortical arousal include psychostimulant drugs; drugs that depress cortical arousal include benzodiazepines, barbiturates, and alcohol.

**Reticular activating system**
System of structures that support arousal in the cerebral cortex

## STOP & CHECK

1. Which part of the cerebral cortex sends movement signals to the body?
2. What parts of the brain are damaged in Parkinson's disease?
3. Which structures are linked to working memory and long-term memory, respectively?

1. The motor cortex 2. Parkinson's disease arises from damage to neurons that begin in the substantia nigra and end in the basal ganglia. 3. The prefrontal cortex is particularly important for working memory; whereas the hippocampus is important for long-term memory.

## Cerebral Blood Flow and Cerebrospinal Fluid

Proper blood flow throughout the brain, called **cerebral blood flow**, is critical for neuron and glial cell function. Highly active brain areas require increased blood flow. When you are working hard on a task such as an exam, your prefrontal cortex is very active. Blood flow increases to the prefrontal cortex to sustain this activity. Blood flow changes throughout the brain when blood capillaries dilate and contract. Highly active cells release a chemical called *nitric oxide* that dilates blood capillaries, which in turn delivers more oxygen.

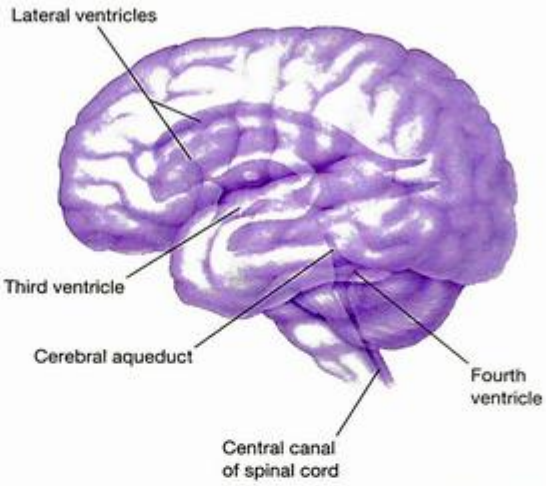
**Cerebral blood flow**
Blood flow throughout the brain

**Cerebrospinal fluid** is a clear fluid that surrounds cells in the brain. Cerebrospinal fluid provides a medium through which nutrients, a sugar called *glucose*, hormones, and other chemicals access brain cells (**Figure 2.15**). In addition to surrounding cells in the brain, cerebrospinal fluid fills many spaces and canals in the

**Cerebrospinal fluid**
Fluid that surrounds cells in the brain

**FIGURE 2.15 Brain Ventricles**

The ventricles are filled with cerebrospinal fluid. The third and fourth ventricles are connected by the cerebral aqueduct. Within the spinal cord, the central canal is filled with cerebrospinal fluid.




brain. The central canal of the spinal cord is filled with cerebrospinal fluid, and there is a smaller canal-like structure in the brain called the *cerebral aqueduct*. The cerebral aqueduct is surrounded by a small layer of tissue called **periaqueductal gray**. The brain also contains cerebrospinal fluid-filled cavities called **ventricles**.

**Periaqueductal gray** Small layer of tissue that surrounds the cerebral aqueduct

**Ventricles** Cerebrospinal fluid-filled cavities in the brain

Cerebrospinal fluid is also found in the *meninges* that surround the brain. Cerebrospinal fluid forms in a layer of the meninges called the *subarachnoid space*. By filling this space, cerebrospinal fluid forms a protective cushion around the brain, protecting it from injury. Cerebrospinal fluid serves as the medium through which drug molecules travel upon crossing into the brain from the blood-brain barrier.

## STOP & CHECK

1. How might thinking be affected if the brain had poor cerebral blood flow?
2. The meninges protect the brain from injury because they contain a clear fluid called _____.

1. Since cells in the brain require oxygen to meet increased energy demands, thinking would certainly be compromised from poor flow. 2. cerebrospinal fluid

## Genes and the Physiological Processes of Cells

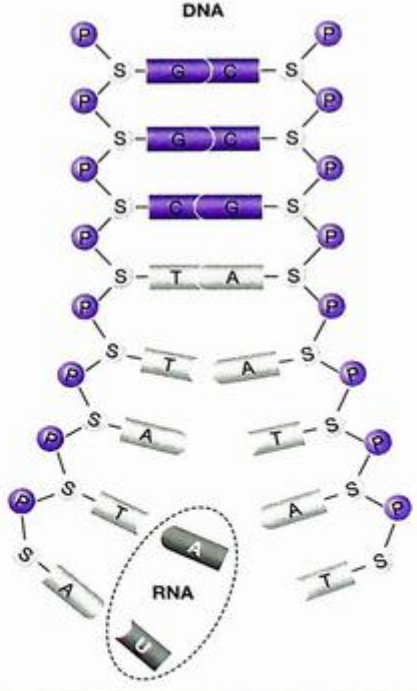
The blueprints for a cell and its functions reside within the cell's nucleus. The nucleus of every cell for humans contains 46 chromosomes. A child inherits 23 chromosomes from each parent. Two of the 46 chromosomes consist of X and Y chromosomes, which determine an individual's sex. If both of these sex chromosomes are X's, then an individual is genetically female. However, if one of these sex chromosomes is a Y, then the individual is genetically male. All of the other chromosomes are called *autosomal chromosomes*.

Each chromosome contains a strand of *deoxyribonucleic acid* (DNA), which contains the specific coding instructions for the basic functions of cells called **genes**. Genes are encoded with the traits we have (**Figure 2.16**). Within this role, genes contain information to synthesize new proteins. Researchers can alter genetic information in animals to study the nervous system (**Box 2.1**).

**Gene**
Segment of DNA encoded with the traits expressed in an organism

**FIGURE 2.16 DNA and RNA**

When a gene is activated, a specific DNA segment is unraveled and transcribed onto ribonucleic acid (RNA), which may then leave the nucleus and carry the transcribed information to ribosomes that synthesize proteins as instructed.



# BOX 2.1

## GENETICALLY MODIFIED ORGANISMS

Genetic technologies allow researchers to characterize the role genes play in behavior and physiological functions. These advances led to the creation of genetically modified invertebrate and vertebrate organisms. For vertebrates, most genetic modification research uses mice, although the development of CRISPR technology (discussed in this chapter's *From Actions to Effects* section) makes the use of genetic modification in other species more feasible.

The genetic modification process starts by injecting genetic material into a pregnant mouse. After the mouse has a litter, researchers test the *genotype*, or genetic makeup, of each mouse pup to identify those with the targeted genetic change. Genetically modified mice fall largely into two categories: transgenic animals and knock-out animals. A *transgenic animal* has either altered genes or additional genetic information. For example, researchers alter amyloid precursor protein genes in transgenic mice to cause production of amyloid plaques, a key neurobiological characteristic found in Alzheimer's disease. A *knock-out animal* fails to express traits from a particular gene; in essence, the gene is "knocked out."

Scientists use a notation system to describe different genotypes for knock-out animals. A heterozygous genotype is noted by a "–/+," with the "–" sign indicating the removed or deactivated gene on one chromosome and the "+" indicating the unaffected gene on the other chromosome. A "+/+" notation, indicating unaffected genes on both chromosomes, describes a nongenetically modified animal, also referred to as a *wildtype*. Animals with a homozygous genotype for a certain trait are noted with a "–/–," indicating a deactivated gene on each chromosome.

For example, serotonin transporter "–/–" knock-out mice exhibit greater levels of the neurotransmitter serotonin in the synaptic cleft and show anxious behavior (Holmes, Li, Murphy, Gold, & Crawley, 2003). The "–/–" describes the deactivation of the serotonin transporter gene on both chromosomes. Thus, these mice completely lack serotonin transporters (serotonin transporters are discussed in Chapter 3). A *phenotype* describes the physiological or behavioral changes caused by a genetic alteration. In this example, enhanced serotonin levels and increased anxiety describe the physiological and behavioral phenotypes for a serotonin transporter knock-out mouse.

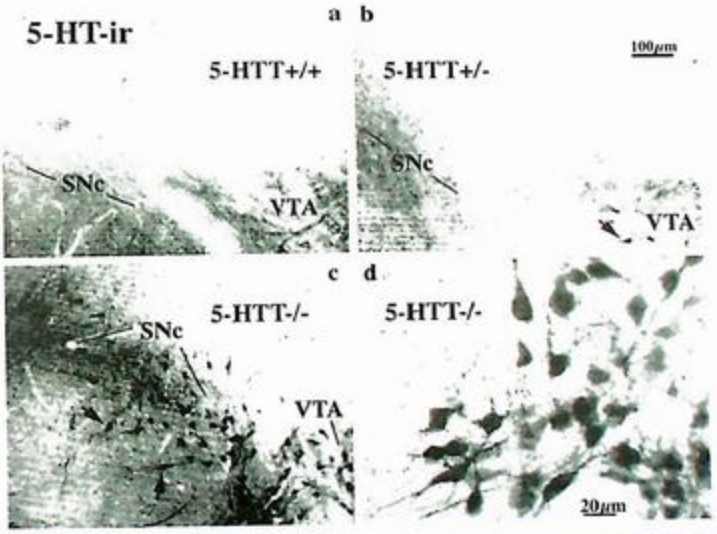
Although transgenic and knock-out data provide important links between genetics and physiological and behavioral activity, scientists keep in mind that genetic alterations may cause unexpected changes during neurodevelopment. In fact, a study by Zhou, Lesch, and Murphy (2002) demonstrated a unique and unexpected consequence of knocking out the serotonin transporter.

In this study, researchers compared serotonin levels in serotonin transporter knock-out mice and confirmed that greater serotonin levels occurred at serotonin synapses, as described previously. However, these researchers also discovered serotonin neurotransmitters inside of neurons that produce the neurotransmitter dopamine. Exploring further, the team found that dopamine transporters had adapted to allow entry of serotonin into dopamine neurons (Zhou et al., 2002). Thus, instead of having mice with an altered serotonin system, they unintentionally produced mice that also had an altered dopamine system (**Box 2.1 Figure 1**).

For these caveats and other reasons, researchers seek to refine and develop new approaches for developing genetically modified organisms. In a variation of the knock-out mouse, researchers have developed *conditional knock-out mice* that have normally functioning genes until a researcher administers a type of enzyme that deactivates a gene. Thus, these mice develop normally but still allow researchers to assess the effects of gene deactivation on some physiological or behavior characteristic. During a study, researchers might wait until mice reach an adult age before administering the enzyme. This technology also allows researchers to specify a particular part of the body to alter the gene, such as a structure within the central nervous system. These and other genetic modification procedures have important implications for understanding the nervous system and for characterizing drug actions and their effects.

**BOX 2.1 FIGURE 1** **Serotonin Transporters on Dopamine Neurons**

Few neurons reveal the neurotransmitter serotonin in the dopamine-rich ventral tegmental area and substantia nigra in wildtype mice (top panel, a). However, in serotonin transporter knock-out mice (bottom panel, c & d), many dopamine neurons contain serotonin. These findings suggest that removal of serotonin transporters led to the nervous system adapting to the loss of serotonin by using dopamine neurons for synthesizing serotonin instead. VTA = ventral tegmental area; 5-HT = serotonin; 5-HTT = serotonin transporter; ir = immunoreactive; the labeling technique used to identify serotonin; SNc = substantia nigra. From Zhou et al. (2002).




Source: Dr. Feng Zhou/Brain Research/Elsevier.

Although genes contain codes to express certain traits such as eye color or production of a particular enzyme, the coding sequence for genes may not be precisely the same from individual to individual. We term these differences *polymorphisms*. A **polymorphism** is a difference in the encoding of a gene compared to the most common sequence in a population. Polymorphisms are common, and determining what type of polymorphism an individual has can aid greatly in understanding a person's response to drug effects. For example, some polymorphisms lead to greater production of certain types of enzymes in the liver. For these individuals, the extra enzymes may break down a drug before it produces any substantial effects.

**Polymorphism** A difference in the encoding of a gene compared to the most common sequence in a population

Activating genes leads to the copying of genetic information, a process referred to as *gene transcription*. A **transcription factor** consists of a substance that increases or decreases gene transcription. During gene transcription, the coding sequence of

**Transcription factor** Substance that increases or decreases gene transcription

a gene copies onto ribonucleic acid (RNA). The type of RNA used to trigger protein synthesis is called *messenger RNA* because it leaves the nucleus and binds to ribosomes in the cell. Ribosomes produce the type of protein specified in the message. Gene transcription is one of many areas studied in the field of **epigenetics**, the study of mechanisms of gene expression not involving alterations to DNA sequences. Future drug therapies may target epigenetic mechanisms for treating neurological or mental disorders (Arango, 2015).

**Epigenetics**
Mechanisms of gene expression not involving alterations to DNA sequences

**Neurogenetics**
How genes support the function of neurons

The field of **neurogenetics** aims to understand how genes support the function of neurons. In doing so, this field also studies how gene mutations, alterations in the DNA sequence for genes, cause neurological disorders, such as Huntington's disease and Alzheimer's disease. For example, neurogenetics studies revealed a mutation in the Huntington gene that leads to the destruction of neurons and subsequently a host of motor and cognitive disturbances in Huntington's disease. The disease is inheritable and ultimately fatal.

We refer to a *Mendelian disease* as one occurring from a single gene mutation inheritable to offspring. Genetic tests arising from neurogenetic studies provide a means for identifying the risk of contracting a Mendelian disease. For example, one can be tested for a mutated Huntington gene that has near 100 percent accuracy before the disease's symptoms occur. Other genetic diseases occur from different types of gene mutations. Sometimes, a mutation occurs as a repeating pattern of nucleotides, the chemical building blocks of DNA, or through an error in replicating or repairing a gene, resulting in *gene duplication*. Many of these diseases can be traced to mutations in multiple genes. For example, *cerebellar ataxia* is a disorder marked by coordination and balance deficits that derives from mutations in over 30 different genes (Jayadev, Smith, & Bird, 2011).

## STOP & CHECK

1. How many chromosomes does a human cell contain?
2. A _____ is a protein that activates a gene.
3. Genetic code is copied onto _____, which delivers the code to ribosomes outside the nucleus.

1. 46 2. transcription factor 3. messenger RNA

## From Actions to Effects: Advances in Therapeutic Use of CRISPR Genetic Technology

Patients suffering from diseases derived from genetic mutations may benefit from emerging genetic technologies to correct or counteract the effects from these mutations. Such efforts require precision genetic alterations, and for this reason, therapeutic genetic strategies increasingly involve the use of CRISPR technology.

CRISPR (pronounced "crisper") is an acronym for *clustered regularly interspaced short palindromic repeats*, referring to sections of DNA that fit this characterization. That is, patterns of DNA are repeated in multiple copies. "Palindromic" refers to a sequence of nucleic acids in one strand of DNA bound to nucleic acids in a matching but opposite order on the second strand of DNA. Spacer DNA refers to noncoding segments of DNA (i.e., DNA that doesn't lead to the production of proteins). Thus, interspaced refers to noncoding DNA that separates the repeated patterns of DNA.

Generally, reference to CRISPR technology includes the use of a protein that can sever bounds in a DNA sequence associated with a particular CRISPR segment. The current leading strategy for therapeutic genetic editing is *Cas9* (CRISPR-associated protein 9). The Cas9 enzyme includes a DNA sequence that will selectively bind to a short sequence of RNA that is copying the genetic code from a specific pattern of DNA linked to a specific CRISPR sequence. This selective targeting is a step up from previous strategies that held the likelihood of affecting genes unrelated to the therapeutic goals of the genetic manipulation. Thus, lacking specificity in genetic editing can cause more harm than good.

At the present time, CRISPR-Cas9 treatments have received fast-track status for review by the U.S. Food and Drug Administration. Recently, the results from a patient with sickle cell disease enrolled in CRISPR-Cas9 clinical trial were aired on CBS's "60 Minutes" (LaPook, 2019). Sickle cell disease caused the patient to experience severe sharp pain throughout her body due to a miscoding of the gene for the hemoglobin protein that caused what should be doughnut-shaped red blood cells to be cells shaped instead like a sickle. The researchers extracted stem cells from the patient's bone marrow and then introduced corrected gene sequences using CRISPR-Cas9. The stem cells were reintroduced into bone marrow and then developed into normal stem cells.

Researchers also use CRISPR-Cas9 approaches to genetically modify animals for the purpose of mimicking human diseases or disorders. In one such study, Horie and colleagues (2018) used CRISPR-Cas9 to prevent the synthesis of the hormone oxytocin in prairie voles. Oxytocin facilitates sociability, among other functions, and prairie voles are well characterized as social animals that are monogamous with mates and raise their pups together. Thus, the researchers sought to determine how the elimination of oxytocin production might affect social attachment among these animals. The researchers measured anxiety, parenting behaviors, sociability toward a familiar vole versus a novel vole, and repetitive behavior. Without oxytocin, voles appeared normal in regard to anxiety and parenting behavior. However, the affected voles did not show a preference between a familiar vole and a novel vole. Moreover, the voles engaged in repetitive behavior. At the conclusion of their report, the authors suggested that the prevention of oxytocin production in the animals led to behaviors—lack of recognition of a familiar vole, repetitive behavior—that appeared in some ways like autism spectrum disorder in humans.

Overall, CRISPR technology holds promise for novel genetic therapies in humans. Further, CRISPR offers innovative approaches for behavioral neuroscience research.

## STOP & CHECK

1. What is the advantage of using CRISPR for genetic therapy in humans?
2. For preclinical research, how does the ability to use genetic manipulation in other species, aside from mice (see Box 2.1), aid in neuroscience research?

1. Genetic manipulation can lead to a host of unintended gene mutations, and thus serious adverse effects, unless high precision can be used for the genetic procedures. CRISPR-Cas9 may meet this "high precision" requirement and, for this reason, is the most promising genetic therapy tool to date. 2. While enormous discoveries about the brain and medical advances have come from mice, this species is not always the best to use for the objectives of the study. In the study about prairie voles presented in this section, researchers desired to closely study prosocial behaviors using genetic manipulation. The voles, they found, exhibited a number of social behaviors found in humans, and therefore, the voles (instead of mice) would provide information that would be more useful to translating their findings to humans.

## CHAPTER SUMMARY

The cells in the central nervous system consist of glial cells and neurons. Neurons consist of dendrites, a soma, an axon, and an axon terminal. Signals from other neurons are received through dendrites, and the message is sent to other neurons from the axon terminal. Glial cells play an important role in supporting the function of neurons.

The nervous system consists of the peripheral nervous system and the central nervous system. The peripheral nervous system consists of the somatic nervous system—for sensory and motor signals—and the autonomic nervous system—for vital functions. The autonomic nervous system consists of the sympathetic, parasympathetic, and enteric nervous systems.

The central nervous system consists of the brain and spinal cord. We divide the brain into subdivisions called the *hindbrain*, *midbrain*, and *forebrain*. The forebrain division is the largest and encompasses the four cortical lobes in the brain called the *occipital lobe* (for vision), the *parietal lobe* (mainly for processing touch information), the *temporal lobe* (for audition and language), and the *frontal lobe* (for cognition and movement). The limbic system consists of the amygdala, hippocampus, cingulate gyrus, thalamus, and hypothalamus. Together these limbic system structures play an important role in emotion. With the exception of olfactory information, which goes directly to the prefrontal cortex, sensory information is received from the head and body and routed through the thalamus to the appropriate lobe for processing. The prefrontal cortex is the most anterior portion of the frontal lobe and the integration center for all sensory information. Motor signals are sent down to the body beginning in the primary motor cortex. The basal ganglia help to regulate voluntary movements.

The cells in the brain receive important sugars and nutrients from the cerebrospinal fluid surrounding these cells and oxygen from blood vessels. Cerebrospinal fluid exists throughout the central nervous system through the central canal in the spinal

cord and through a network of ventricles and the cerebral aqueduct in the brain. Cerebral blood flow increases in active parts of the brain.

The basic functions and development of cells are directed by genes, which are segments of DNA. Molecules that activate genes are called *transcription factors*. Gene activation causes a copy of a gene to be imprinted on RNA. RNA directs production of protein synthesis through ribosomes found outside of the cell's nucleus.

## KEY TERMS

Neurons 29
Glial cells (or glia cells) 29
Dendrites 31
Axons 31
Synapse 32
Interneuron 32
Sensory neurons 32
Motor neurons 32
Oligodendrocytes 32
Astrocytes 32
Microglial cells 32
Somatic nervous system 36
Autonomic nervous system 37
Sympathetic nervous system 37
Parasympathetic nervous system 37
Enteric nervous system 37
Cerebral cortex 39
Medulla 40
Hypothalamus 42
Limbic system 42
Nucleus accumbens 43
Occipital lobe 43
Temporal lobe 44
Parietal lobe 44
Frontal lobe 44
Prefrontal cortex 44
Thalamus 44
Motor cortex 45
Basal ganglia 46
Pons 46
Cerebellum 46
Hippocampus 47
Reticular activating system 47
Cerebral blood flow 47
Cerebrospinal fluid 47
Periaqueductal gray 48
Ventricles 48
Gene 49
Polymorphism 51
Transcription factor 51
Epigenetics 52
Neurogenetics 52

# Neurotransmission

## Chapter Outline

- Electrical Events Within a Neuron and the Release of Neurotransmitters
- Electrical Potentials Along Axons
- Propagation of Action Potentials Down Axons
- Neurotransmitters: Signalling Molecules for Neuronal Communication
- Neurotransmitters and Receptors
- Types of Neurotransmitters
- Other Types of Chemical Transmission in the Nervous System
- From Actions to Effects: Probiotics and Mental Health

## Learning Objectives

- Explain the process of electrical potentials within neurons
- Explain the process of chemical neurotransmission
- Contrast ionotropic and metabotropic receptors
- State neurotransmitters important for psychoactive drugs, including their synthesis steps and receptors
- Discuss the role of microbiota in neural communication

**Neurotransmission** is the transmission of information between neurons. Neurotransmission typically involves a neuron releasing chemicals called *neurotransmitters* into a synapse, which allows these neurotransmitters to act on sites on another neuron. The study of neurotransmission includes looking at events inside

**Neurotransmission**
Transmission of information between neurons

the neuron that cause the production and release of neurotransmitters as well as the actions neurotransmitters have on sites situated on other neurons.

## Electrical Events Within a Neuron and the Release of Neurotransmitters

**Electrical potential**
Difference between the electrical charge within a neuron versus the electrical charge of the environment immediately outside the neuron.

**Depolarization**
Reduced difference between the positive and negative charges on each side of a membrane.

**Hyperpolarization**
Increased difference between the positive and negative charges on each side of a membrane.

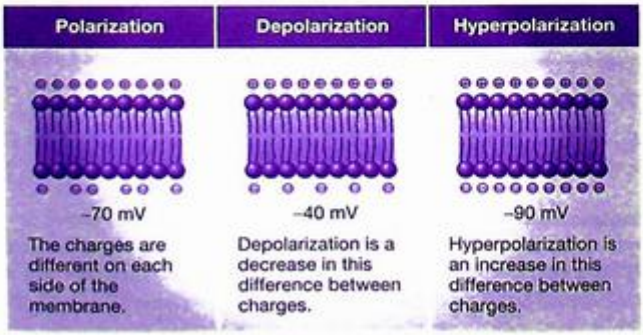
Certain electrical events within a neuron must take place before neurotransmitters can be released. These events consist of a series of *action potentials* (discussed later in the chapter). Action potentials begin at an axon hillock and proceed down the length of an axon.

For a neuron, an **electrical potential** is a difference between the electrical charge within a neuron and the electrical charge of the environment immediately outside the neuron. Normally, the electrical charge within a neuron is negative compared to the outside environment. This characteristic leaves the neuron's membrane polarized, meaning that on one side the charge is negative, but on the other side, the charge is positive, similar to the negative and positive poles of a magnet (**Figure 3.1**). The term **depolarization** describes a reduced difference between the positive and negative charges on each side of a membrane. The term **hyperpolarization** describes an increased difference between the positive and negative charges on each side of a membrane.

**Review!** A neuron has many dendrites and a single axon. A synapse consists of an axon terminal, the synaptic cleft, and the postsynaptic terminal (Chapter 2).

**FIGURE 3.1 Polarization, Depolarization, and Hyperpolarization**

During the resting potential, an electrical polarization is maintained because of a concentration of negatively charged ions and negatively charged proteins.



The term *local potential* refers to an electrical potential on a specific part of a neuron. The local potential changes in response to events within a neuron and with communication from other neurons. Local potentials change as charged particles (*ions*) move in and out of the neuron through pores called **ion channels**. The influence on local potentials from other neurons occurs as either an excitatory postsynaptic potential or an inhibitory postsynaptic potential. An *excitatory postsynaptic potential* depolarizes a local potential, whereas an *inhibitory postsynaptic potential* (IPSP) hyperpolarizes a local potential. Researchers study local potential changes using electrophysiological procedures as described in **Box 3.1**.

**Ion channels**
Pores in a neuronal membrane that allow the passage of ions

# BOX 3.1

## ELECTROPHYSIOLOGY AND MICRODIALYSIS

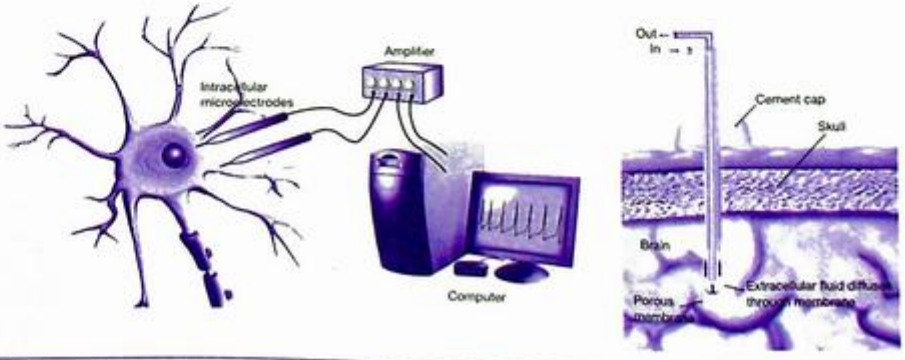
A research technique called *electrophysiology* uses electrodes to measure or stimulate potentials on neuronal membranes. Electrophysiology procedures use either macroelectrodes or microelectrodes. *Macroelectrodes* record the activity of thousands of neurons within a structure. They also can be used as a stimulator to activate thousands of neurons within a structure.

*Microelectrodes* provide a precise assessment or stimulation of either just a few or even single neurons (**Box 3.1 Figure 1, left panel**). The use of a microelectrode to measure potentials within a single neuron is called *intracellular recording*. In particular, researchers use intracellular recording to measure action potentials. This technique allows a neuron's firing rate to be calculated. Although electrophysiological techniques can assess the activity of neurons, they cannot determine the amount of neurotransmitter released from a neuron.

*Microdialysis* procedures, however, can be used to sample neurotransmitter levels (**Box 3.1 Figure 1, right panel**). Microdialysis probes have a semipermeable membrane.

**BOX 3.1 FIGURE 1** **Electrophysiology and Microdialysis**

Researchers can use microelectrodes to both stimulate and record potential changes in neurons (left). Researchers use microdialysis probes to sample cerebrospinal fluid from the brain (right). They then determine the amount of certain chemicals, such as neurotransmitters, in the microdialysis samples.




(Continued)

charged sodium ($Na^+$) ions prevent $Na^+$ from entering the neuron. $Na^+$ channels are **voltage-gated ion channels**, meaning that the opening or closing of these channels depends on local potential changes. $Na^+$ channels open in response to depolarization, which is why they generally remain closed during the resting potential.

**Voltage-gated ion channels** Channels that open or close, depending on local potential changes

We do find channels open for the positively charged ion potassium ($K^+$) during the resting potential, however. The negative charge within the neuron attracts positively charged $K^+$ ions into the neuron, a property called *electrostatic attraction*. Yet at some point, $K^+$ ions cease entering the neuron because ions of the same type resist being concentrated, a property called a *concentration gradient*. Thus, as $K^+$ becomes more concentrated within the neuron, some $K^+$ ions exit the neuron due to a concentration gradient. The balance between the electrostatic attraction and concentration gradient repulsion facilitates a relatively constant resting potential.

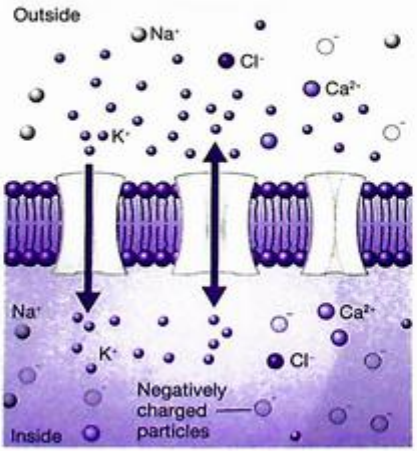
This back-and-forth of $K^+$ leaves the charge of the resting potential relatively constant, but not perfectly constant. Small depolarizations occur as the charge slightly fluctuates, causing nearby $Na^+$ channels to open. The opened $Na^+$ channels allow a small concentration of $Na^+$ ions to leak into the neuron. If left unchecked, a buildup of $Na^+$ would further depolarize the neuron beyond its normal resting potential.

**Sodium–potassium pump** Neuronal membrane mechanism that brings two $K^+$ ions into the neuron while removing three $Na^+$ ions from the neuron.

To prevent these excess $Na^+$ ions from changing the resting potential, neuronal membranes contain sodium–potassium pumps. A **sodium–potassium pump** is a neuronal membrane mechanism that brings two $K^+$ ions into the neuron while removing three $Na^+$ ions from the neuron (**Figure 3.3**). By removing more $Na^+$ ions than the $K^+$ ions brought in, this pumping activity results in a net negative charge.

## FIGURE 3.2 Resting Potential

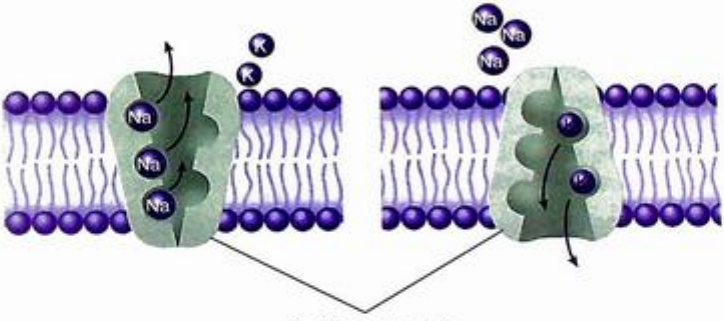
During the resting potential, an electrical polarization is maintained because of a concentration of negatively charged ions and negatively charged proteins. Potassium ($K^+$) ions can enter and leave the neuron through open $K^+$ channels.

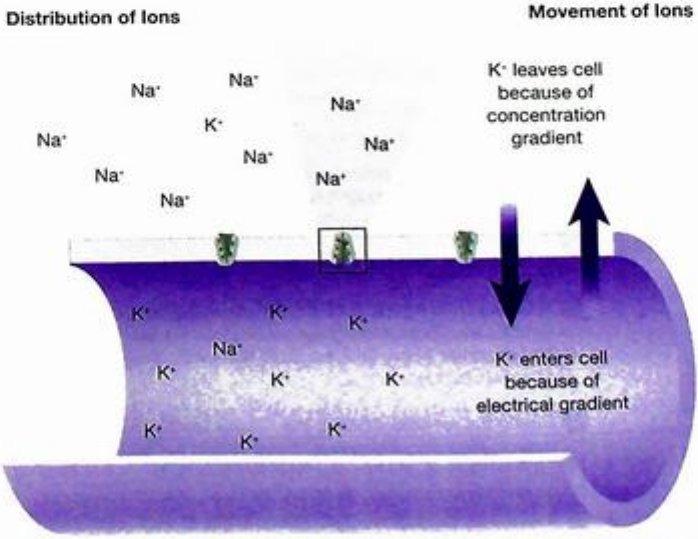


This activity facilitates rapid adjustments to small depolarizations occurring during the resting potential and, in turn, closes $Na^+$ channels. Researchers refer to the small potential changes that occur during the resting potential as *electrotonic potentials*. Thus, processes occur to maintain the resting potential at a certain level of polarization, preventing the potential charge from reaching a threshold value that would trigger an action potential.

**FIGURE 3.3 Sodium–Potassium Pump**

The sodium–potassium pump helps maintain a resting potential by removing three $Na^+$ ions for every two $K^+$ ions brought in.



When an excitatory postsynaptic potential occurs, depolarization causes local $Na^+$ channels to open, allowing for a larger concentration of $Na^+$ ions in the neuron. If no other excitatory postsynaptic potentials occur, then depolarization quickly ends and a resting potential resumes. If multiple excitatory postsynaptic potentials occur in short succession, an *action potential* occurs.

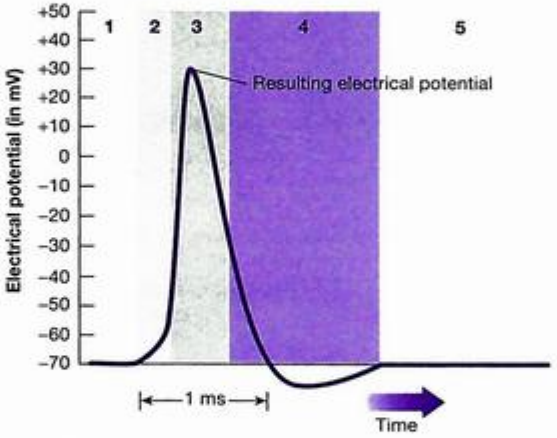
**Action potential** Rapid depolarization, causing the charge in the neuron to become temporarily positive

## Action Potential

An **action potential** is a rapid depolarization that causes the charge in the neuron to become temporarily positive (**Figure 3.4**). The action potential occurs when all

**FIGURE 3.4 Electrical Impulse Within a Neuron**

Electrical impulses within neurons occur in several stages, and each stage depends on the opening or closing of voltage-gated ion channels.




1. During the resting potential stage, the membrane is only permeable to $K^+$ through having open $K^+$ channels.
2. As depolarization occurs, the membrane becomes permeable to $Na^+$ ions through opening $Na^+$ channels.
3. An action potential occurs if polarization meets a specific threshold. During the action potential stage all $Na^+$ channels open, causing rapid $Na^+$ influx. Then $Na^+$ channels reclose.
4. During the refractory period the $K^+$ ions rapidly exit the neuron, returning a negative charge within the neuron. During the refractory period, the neuron resists producing another action potential.
5. After the refractory period, the neuron returns to a resting potential.

$Na^+$ ion channels open for that portion of the axon membrane, resulting in a rapid influx of $Na^+$ into the neuron. After opening during an action potential, the $Na^+$ channels close after 1 to 3 milliseconds. The short duration of time for an open $Na^+$ channel limits the degree of positive electrical charge to a certain value. As the example shows in Figure 3.4, the action potential reached a height of +130 mV. These properties are described by the **all-or-none law**, which states that the magnitude of an action potential is independent from the magnitude of potential change that elicited the action potential. The action potential ends immediately after the $Na^+$ channels close.

**All-or-none law**
Magnitude of an action potential is independent from the magnitude of potential change that elicited the action potential

## Refractory Periods

The **refractory period** is a short duration of time following an action potential when the neuron resists producing another action potential (Figure 3.4). The refractory period is divided into two phases: the *absolute refractory period* and the *relative refractory period*. During the absolute refractory period, consisting of 1–2 milliseconds, the neuron is incapable of producing another action potential. During this period, $K^+$ ions rapidly exit the neuron through open $K^+$ channels, returning the local potential to negative again. In fact, the negative charge is initially more negative than the resting potential charge. Because the $Na^+$ channels remain closed during the absolute refractory period, no amount of depolarization can produce another action potential. During the relative refractory period, lasting 2–4 milliseconds after the absolute refractory period, the local potential remains hyperpolarized, but a sufficiently strong level of stimulation can open $Na^+$ channels and generate another action potential.

**Refractory period**
Period following an action potential when the neuron resists producing another action potential

## STOP & CHECK

1. Depolarization is a decrease in potential, whereas hyperpolarization is a(n) _____ in potential.
2. To prevent small concentrations of $Na^+$ from altering a resting potential, a(n) _____ expels $Na^+$ from the neuron.
3. When membrane depolarization meets a specific threshold value, all $Na^+$ channels open, resulting in a massive depolarization called a(n) _____.
4. After the action potential, $K^+$ channels open, causing $K^+$ to rapidly _____ the neuron.

1. increase 2. sodium–potassium pump 3. action potential 4. leave (or exit, etc.)

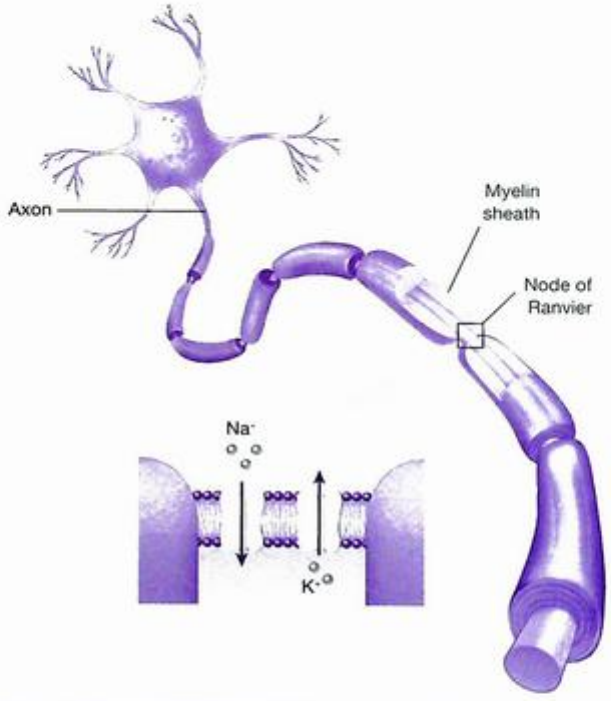
## Propagation of Action Potentials Down Axons

The **propagation of action potentials** refers to a series of action potentials occurring in succession down an axon. The propagation of action potentials begins at the axon hillock. Once this begins, each depolarization produced by an action potential causes another action potential to occur further down the axon until reaching the axon terminal (**Figure 3.5**). Action potentials propagate in only one direction

**Propagation of action potentials**
Series of action potentials occurring in succession down an axon

**FIGURE 3.5 Action Potentials on Myelinated Axons**

On myelinated axons, action potentials occur at each node of Ranvier. Action potentials only propagate down the axon because the previous $Na^+$ channels remain in a refractory period.




because the preceding portion of an axon is in a refractory period. The number of action potentials occurring per unit of time, usually milliseconds, is called a **firing rate**.

**Firing rate** The number of action potentials occurring per unit of time, usually in milliseconds

Myelin sheathing increases the speed of conductance down the axon. Sections of myelin sheaths surround most vertebrate axons. The uncovered sections of axons between myelin sheaths are called **nodes of Ranvier** (pronounced RAHN-vee-ay). Each node contains $K^+$ channels and a high density of $Na^+$ channels. An action potential occurring at one node produces a strong depolarizing current, which is passively conducted down the myelinated segment of axon, affecting the next node. At the next node, the depolarizing current causes another action potential, and the process continues (Figure 3.5). The jumping of action potentials from one node to another is referred to as *saltatory conduction*.

**Nodes of Ranvier** Uncovered sections of axons between myelin sheaths

## STOP & CHECK

1. Sodium and potassium channels are located down the length of an axon, facilitating the propagation of _____ potentials.
2. The number of action potentials occurring during a certain period of time is called a(n) _____.
3. Axons with _____ sheathing have a greater speed of conductance compared to axons without myelin sheathing.

1. action 2. firing rate 3. myelin

## Neurotransmitters: Signalling Molecules for Neuronal Communication

Once action potentials reach the axon terminal, a series of events occurs that ultimately causes the release of neurotransmitters. **Neurotransmitters** are signalling chemicals that are synthesized within neurons, are released from neurons, and have effects on neurons or other cells. Neurotransmitters serve as the mode for chemical neurotransmission between neurons that involves a series of stages, beginning with the synthesis of neurotransmitters and ending with the release of neurotransmitters (**Figure 3.6**). Chemical neurotransmission consists of the main focus in psychopharmacology, as the actions of psychoactive drugs depend upon changes in chemical neurotransmission. Another form of neural communication is *electrical neurotransmission*. Electrical neurotransmission consists of a neuron transferring ions to another neuron via ion channels, allowing for rapid communication between neurons. Electrical neurotransmission occurs within many brain structures, but is less prominent than chemical neurotransmission.

**Neurotransmitters**
Signalling chemicals that are synthesized within neurons, are released from neurons, and have effects on neurons or other cells

### Neurotransmitter Synthesis

Neurotransmitters are synthesized from other molecules with the aid of enzymes. Generally, smaller neurotransmitter molecules such as acetylcholine and dopamine are synthesized in the axon terminal. Larger neurotransmitter molecules such as neuropeptide neurotransmitters are synthesized in the soma.

### Neurotransmitter Storage

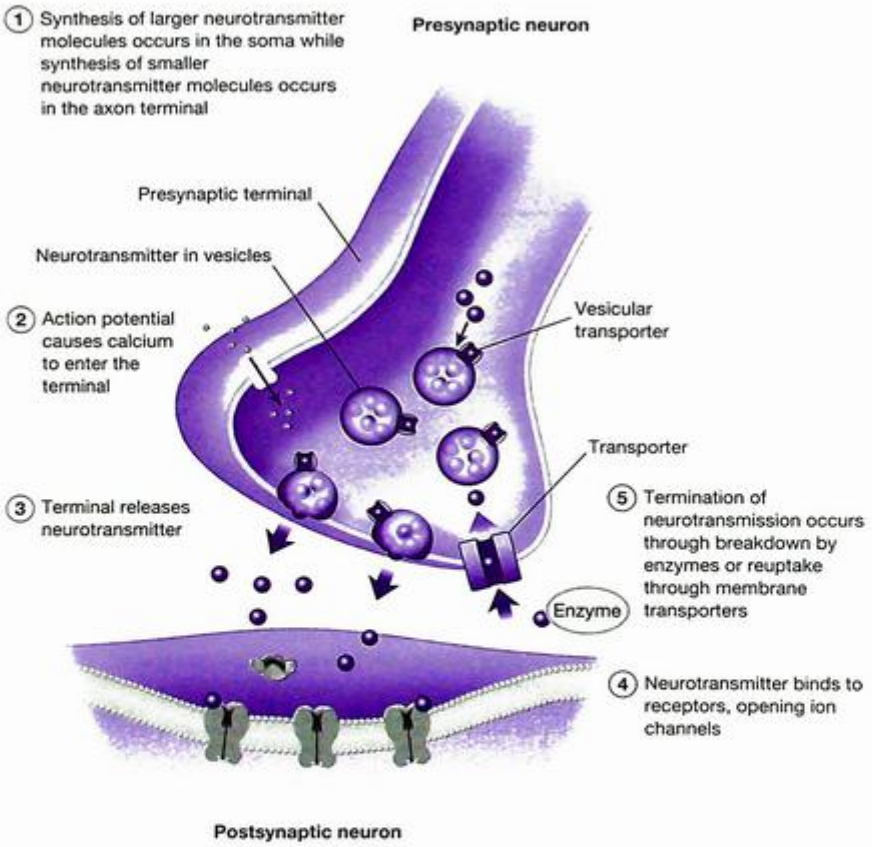
**Synaptic vesicles** (or **neurotransmitter vesicles**) store and protect neurotransmitters after synthesis. Neurotransmitters enter vesicles through channels called **vesicular transporters** (Figure 3.6). Synaptic vesicles protect neurotransmitters from being destroyed by enzymes and prevent neurotransmitters from being released prematurely. Storing neurotransmitters in this manner allows for immediate release during neurotransmission.

**Synaptic vesicle (or neurotransmitter vesicle)**
A vesicle that stores and protects neurotransmitters

**Vesicular transporter**
Channel located on a vesicle that allows passage of neurotransmitters

**FIGURE 3.6 Chemical Neurotransmission**

Chemical neurotransmission occurs in many steps, including neurotransmitter synthesis, release, receptor binding, and termination.




Vesicles already in the axon terminal store small molecule neurotransmitters, whereas vesicles in the soma store large molecule neurotransmitters. Microtubules in the axon then transport vesicles from the soma to the axon terminal. Not every neurotransmitter is stored after synthesis, however. For example, the endocannabinoid neurotransmitter anandamide is not stored in vesicles (Placzek, Okamoto,

Ueda, & Barker, 2008). Without a storage mechanism, anandamide escapes from the neuron immediately after synthesis.

## Calcium Influx and Neurotransmitter Release

Once an action potential occurs in the axon terminal, voltage-gated calcium ($Ca^{2+}$) channels open, allowing $Ca^{2+}$ to enter the axon terminal. Calcium causes **exocytosis**, the fusing of synaptic vesicles to the axon terminal membrane and the release of stored neurotransmitters into the synaptic cleft (Figure 3.6). After fusing with the membrane, the vesicles recede into the terminal and are refilled with neurotransmitters. However, vesicles for neuropeptides are returned empty to the soma to be filled again with neuropeptides.

**Exocytosis**
Fusing of synaptic vesicles to the axon membrane and release of stored neurotransmitters into the synaptic cleft

## Neurotransmitters Bind to Receptors

Neurotransmitters released into the synaptic cleft bind to receptor proteins, which may be located on the postsynaptic terminal, axon terminal, or both (Figure 3.6). The binding of a neurotransmitter causes a *conformational change* in the receptor to occur. Receptor proteins, like other proteins, are composed of long strings of amino acids; the inward folding and shapes produced from the string form a receptor's conformation. The change in a receptor's conformation caused by a neurotransmitter subsequently leads to changes taking place in the neuron.

## Termination of Neurotransmission

After a neurotransmitter releases from a receptor, one of a number of processes occurs to prevent the neurotransmitter from binding to other receptors in the synapse (Figure 3.6). These processes serve to end neurotransmission. For one of these processes, enzymes break down a neurotransmitter into different molecules referred to as *metabolites*. This process is called **catabolism**. Because these new molecules do not match to a neurotransmitter's receptor, neurotransmission effectively stops.

We also use the term **turnover** to refer to the conversion of a neurotransmitter to a metabolite. Researchers infer the rate of neurotransmitter release based on metabolite levels from turnover. For example, high levels of the dopamine metabolite DOPAC (stands for "3,4-Dihydroxyphenylacetic acid") in cerebrospinal fluid indicate that neurons produced a large amount of dopamine, since catabolism of dopamine produces DOPAC. Knowing the amount of turnover occurring after administering a drug informs researchers about the levels of neurotransmission that account for the drug's effects.

During another process called **reuptake**, membrane transporters on axon terminals return neurotransmitters to the axon terminal. Vesicles then store the neurotransmitters for later release. In essence, reuptake serves as a recycling program for neurons. Finally, neurotransmitters may be transported from the synaptic cleft into an astrocyte glial cell. Afterward, enzymes within the glial cell catabolize the neurotransmitters.

**Catabolism**
Process involving the enzymatic breakdown of neurotransmitters and other molecules

**Turnover of neurotransmitters**
The conversion of a neurotransmitter to a metabolite

**Reuptake**
Return of neurotransmitters to the axon terminal via membrane transporters

## STOP & CHECK

1. After synthesis, a neurotransmitter may be stored in a(n) _____ until released from the neuron.
2. Neurotransmitters are released from a neuron after the influx of _____, which is caused by an action potential.
3. Neurotransmitters bind to and activate _____, which may be on the postsynaptic terminal, axon terminal, or both.
4. Neurotransmission can be terminated through enzymatic breakdown (i.e., catabolism), transportation into a glial cell, or through _____ of neurotransmitters.

1. vesicle 2. calcium 3. receptors 4. reuptake

## Neurotransmitters and Receptors

**Receptor**
Protein located in a neuron membrane that can be bound to and activated by a neurotransmitter

**Ligand**
A molecule that binds to a protein

**Receptors** are proteins located in neuron membranes that can be bound to and activated by neurotransmitters. Receptors match to a specific neurotransmitter. Thus, the neurotransmitter dopamine, for example, will bind only to dopamine receptors, but cannot bind to receptors for other neurotransmitters, such as receptors for acetylcholine, serotonin, or glutamate. Neurotransmitters are **ligands**, a term that refers to a molecule that binds to a protein.

### Postsynaptic and Presynaptic Receptors

Researchers characterize receptors not only by the neurotransmitter they match to but also by their location within a synapse. The terms *presynaptic* and *postsynaptic* describe the locations for receptors in a synapse. Receptors located on the postsynaptic terminal are called *postsynaptic receptors*, and receptors located on the axon terminal are called *presynaptic receptors*.

**Autoreceptor**
Presynaptic receptor that is activated by neurotransmitters released from the same axon terminal

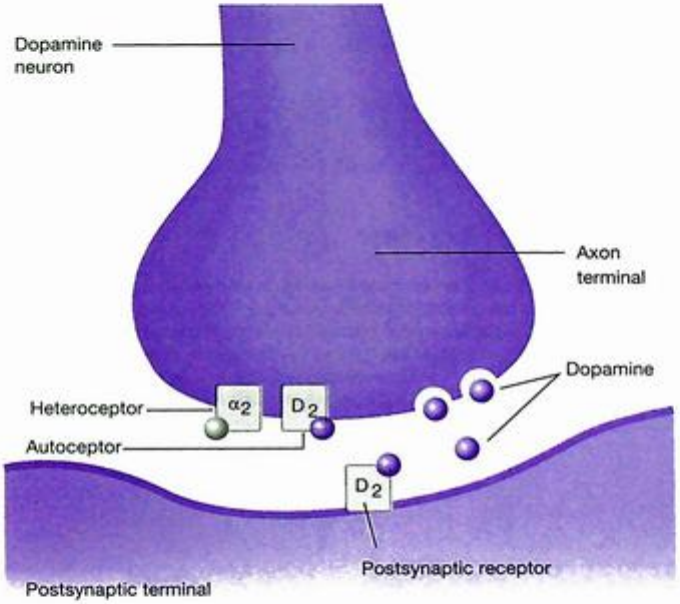
Presynaptic receptors have two types. The first type is an **autoreceptor**, a presynaptic receptor activated by neurotransmitters released from the same axon terminal (**Figure 3.7**). Activating an autoreceptor usually inhibits neurotransmitter release. This particular action serves to limit the amount of neurotransmitter released. One of the receptors for the neurotransmitter dopamine functions as an autoreceptor. When released from an axon terminal, dopamine binds to this autoreceptor, reducing the amount of dopamine released.

**Heteroceptor**
Presynaptic receptor that is activated by neurotransmitters different from those released from the axon terminal

The second type of presynaptic receptor is a **heteroceptor**, a presynaptic receptor that is activated by neurotransmitters different from those released from the axon terminal (Figure 3.7). Heteroceptors may increase or decrease neurotransmitter release. For example, a heteroceptor for the neurotransmitter norepinephrine is located on axon terminals for the neurotransmitter dopamine. Binding to this receptor reduces dopamine release.

**FIGURE 3.7 Presynaptic Receptors**

Receptors on the presynaptic terminal (i.e., axon terminal) influence neurotransmitter release. Autoreceptors are activated by the neurotransmitter released from the terminal, whereas a heteroceptor is activated by a different neurotransmitter. On the dopamine neuron shown here, the $D_2$ autoreceptor is activated by dopamine, whereas the $\alpha_2$ heteroceptor is activated by norepinephrine. Presynaptic receptors may inhibit or excite activity within the presynaptic terminal, which may decrease or increase neurotransmitter release, respectively. Both $D_2$ autoreceptors and noradrenergic (i.e., norepinephrine) $\alpha_2$ heteroceptors are known to inhibit neurotransmitter release.




## Neurotransmitter Receptors Are Ionotropic or Metabotropic

In addition to synaptic location, we identify receptors by their structure. In this way, we distinguish between two primary types of neurotransmitter receptors: *ionotropic receptors* and *metabotropic receptors*. **Table 3.1** summarizes the differences between these two types of receptors.

**Ionotropic receptors** are ion channels that open when a matching neurotransmitter binds to a site on the channel (**Figure 3.8**). In this regard, ionotropic receptors act as *ligand-gated* ion channels, with the neurotransmitter serving as the ligand. An ionotropic receptor comprises subunits that span the neuronal membrane. The subunits form a ring that comprises the channel. The shifting of these subunits causes the channel to open or close. The channel opens with a neurotransmitter, binds to the receptor, and then closes once the neurotransmitter leaves the receptor.

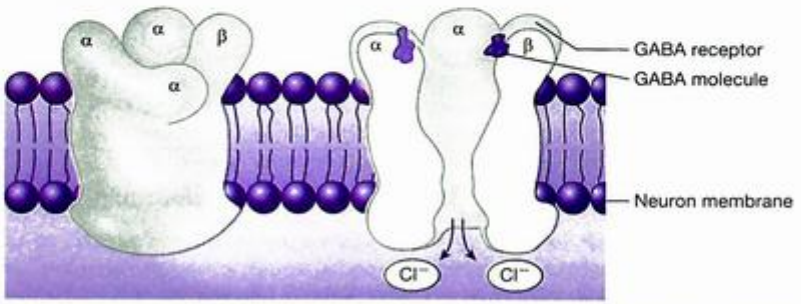
**Ionotropic receptor**
Ion channel that opens when a matching neurotransmitter binds to a site on the channel

**TABLE 3.1 Differences Between Ionotropic and Metabotropic Receptors**

| | Ionotropic Receptor | Metabotropic Receptor |
|---|---|---|
| Proximity to effectors | Attached to ion channel | Separated from ion channels, enzymes, and second messengers |
| Type of effect | Opens the ion channel | Uses a G protein as the first step toward activating ion channels, effector enzymes, and second messengers |
| Duration of effect | Effect ends when neurotransmitter leaves the binding site | Effects persist after the neurotransmitter leaves receptor |
| Impact on a neuron | Changes local potential, causing depolarization or hyperpolarization | Can affect local potentials, enzyme regulation, gene activation, and protein synthesis |

**FIGURE 3.8 Ionotropic Receptor**

An ionotropic receptor consists of an ion channel with a neurotransmitter binding site. The receptor shown here is activated by the neurotransmitter γ-aminobutyric acid (GABA) and is called the $GABA_A$ receptor. $GABA_A$ receptor activation causes an IPSP by allowing negatively charged chloride ($Cl^-$) ions into the neuron. The $GABA_A$ receptor shown here also has binding sites for different chemical substances, such as benzodiazepines. These other binding sites serve to modify the receptor's function, including how well GABA activates the receptor.



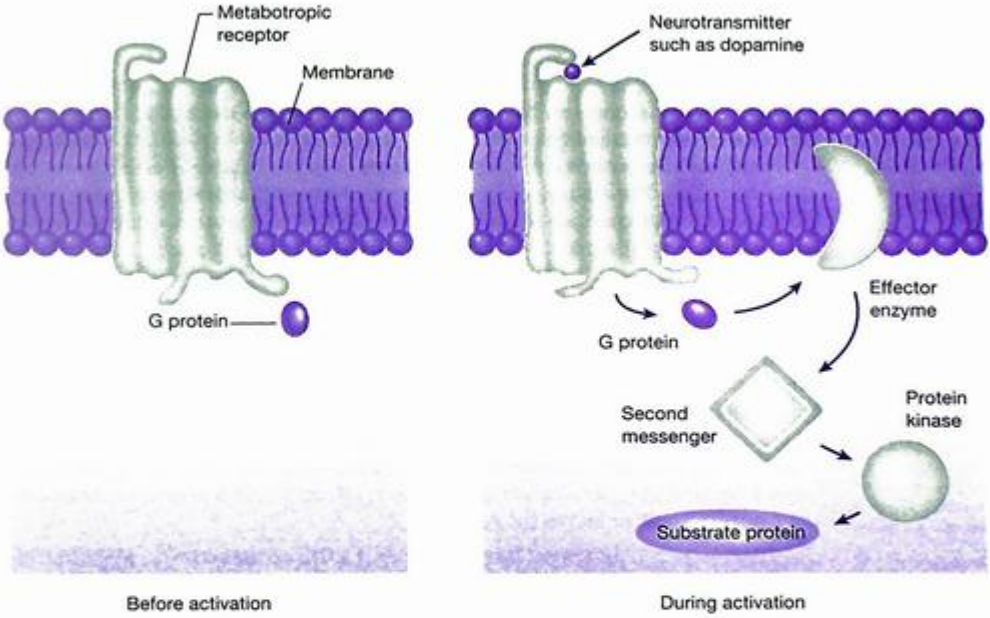

Source: Based on Guidotti et al. (1983).

**Metabotropic receptor**
Receptor physically separated from parts of the neuron where the receptor exerts its effects

**A metabotropic receptor** is physically separated from parts of the neuron where the receptor exerts its effects (**Figure 3.9**). Unlike an ionotropic receptor, which consists of an ion channel with a neurotransmitter binding site, many metabotropic receptors rely on a G protein to convey effects to channels or other parts of the neuron. Given this, we also refer to most metabotropic receptors as *G protein-coupled*

**FIGURE 3.9 Metabotropic Receptor**

A metabotropic receptor relies on a G protein to carry out effects within the neuron. Through the activation of a G protein (right), a cascade of biological events, collectively referred to as *intracellular signalling*, may occur within the neuron, including the activation (or inhibition) of ion channels or activation of effector enzymes. The activation of effector enzymes produces second messengers. Second messengers, in turn, activate protein kinases and substrate proteins (right).




*receptors*. Other metabotropic receptors are receptor tyrosine kinases, discussed in "Other Types of Chemical Transmission in the Nervous System" later in this chapter.

A **G protein** for a metabotropic receptor resides within the neuron, in close proximity to the receptor. The G protein consists of three subunits, referred to as alpha ($\alpha$), beta ($\beta$), and gamma ($\gamma$). These subunits remain attached to each other until a neurotransmitter activates the receptor. Activating the receptor causes the G protein to separate into two sections, the $\alpha$ subunit and a $\beta\gamma$ combination (referred to as a *dimer*). After a period of time, the subunits return to a three-subunit state, essentially deactivating the receptor. Box 4.2 in Chapter 4 describes a research technique used to characterize the activation and inactivation process for G proteins.

**G protein**
A three-subunit protein that carries out effects of a metabotropic receptor

After an activated receptor causes G protein subunits to separate, the separated subunits may cause a variety of effects within a neuron, collectively referred to as *intracellular signalling* (Figure 3.9). First, the free subunits can activate ion channels such

as $K^+$ or $Ca^{2+}$ ion channels on the neuronal membrane, changing the flow of ions into or out of the neuron. Second, the free subunits can activate **effector enzymes**, which leads to the production of *second messenger* molecules. Common effector enzymes include adenylyl cyclase, phospholipase C, phospholipase A2, and phosphodiesterase.

**Effector enzymes** Enzyme that produces second messenger proteins

A **second messenger** is an intracellular signalling molecule produced following the activation of another protein by an extracellular molecule (for example, a neurotransmitter). Common second messengers include cyclic adenosine monophosphate (cAMP), cyclic guanosine monophosphate (cGMP), phosphoinositide, and calcium. A second messenger molecule will activate a protein, called a *protein kinase*.

**Second messenger** Intracellular signalling molecule produced following the activation of another protein by an extracellular molecule, such as a neurotransmitter

When using the term *second messenger*, you can think of the neurotransmitter that activated the receptor as the *first messenger*. Thus, the first messenger (the neurotransmitter) binds to the receptor protein. Through the steps described above, the subsequent production of a second messenger molecule leads to the activation of an intracellular protein kinase.

A **protein kinase** is an enzyme that causes phosphorylation of a substrate protein (see below). Phosphorylation is a common process for activating proteins, which involves adding at least one phosphoryl group ($-PO_3^{-2}$) to a protein. Common protein kinases include protein kinase A, protein kinase G, protein kinase C, and calcium/calmodulin kinase.

**Protein kinase** Enzyme that causes phosphorylation of a substrate protein

A protein kinase activates a substrate protein. A **substrate protein** can be an ion channel, an enzyme involved in the making of neurotransmitters, a neurotransmitter receptor, or other proteins within the neuron. A substrate protein also can be a transcription factor. Two common transcription factors for neurons are c-fos and cAMP response element-binding (CREB) protein. The activation of genes may lead to the synthesis of proteins within the neuron, including receptors for neurotransmitters and enzymes used in neurotransmitter synthesis. Given that a series of events may occur after activating a metabotropic receptor, effects within a neuron continue after the neurotransmitter leaves the receptor.

**Substrate protein** Protein, following activation of a protein kinase, that may consist of an ion channel, enzyme, neurotransmitter receptor, or other proteins involved in neuronal processes

**Review!** A transcription factor activates or deactivates a gene (Chapter 2).

# STOP & CHECK

1. Where is an autoreceptor located?
2. How does a voltage-gated ion channel differ from a ligand-gated ion channel?
3. A metabotropic receptor requires the activation of a _____ protein as the first step for intracellular signalling.
4. After being activated by a second messenger, a protein kinase can affect the functioning of a neuron in a variety of ways, including acting as a _____ to alter gene expression.

1. An autoreceptor is located on an axon terminal and is activated by the neurotransmitters released from the same axon terminal. 2. A voltage-gated ion channel opens when a certain local potential occurs, whereas a ligand-gated ion channel opens when a neurotransmitter binds to it. 3. G (as in G-protein) 4. transcription factor

## Types of Neurotransmitters

Dozens of neurotransmitters have so far been identified in the nervous system. **Table 3.2** lists the neurotransmitters most important for psychoactive drugs, and therefore consist of those covered in this textbook. Table 3.2 groups neurotransmitters by chemical structure. For example, dopamine, norepinephrine, and serotonin belong in the monoamine category because they have a single amine chemical group, $-NH_2$, in their structures.

The synthesis of neurotransmitters most often occurs from the conversion of amino acids. Amino acids come from our diet, but also from production in the body. The term **essential amino acid** refers to an amino acid that must come from our diet or a microbial source, whereas the term *nonessential amino acid* refers to an amino acid the body produces. Bacteria in the gut also produce amino acids, including some essential amino acids, such as tryptophan, which then enter the circulatory system and cross the blood–brain barrier to reach the brain (Sharon et al., 2014). This chapter includes the synthesis steps for many of the neurotransmitters listed in Table 3.2.

**Essential amino acid**
Amino acid that is not produced in the body and must come from diet

### Glutamate and GABA Are the Most Abundant Neurotransmitters

While amino acids generally serve as precursors for synthesizing proteins, some amino acids serve as neurotransmitters. The amino acid neurotransmitters glutamate and GABA are found throughout the nervous system. **Glutamate** is the most prominent member of a small amino acid family called *excitatory amino acid neurotransmitters*. The amino acid **GABA** is the most prominent member of a small amino acid family called *inhibitory amino acid neurotransmitters*.

**Glutamate**
Excitatory amino acid neurotransmitter

**GABA**
Inhibitory amino acid neurotransmitter

**TABLE 3.2** Neurotransmitter Categories and Selected Neurotransmitters

| Amino Acids | Neuropeptides |
|---|---|
| gamma-aminobutryic acid (GABA) | Endorphins |
| glutamate | |
| **Acetylcholine** | **Gases** |
| | Nitric oxide |
| **Monoamines** | |
| Catecholamines | |
| dopamine | |
| norepinephrine | |
| epinephrine | |
| Indoleamines | |
| serotonin | |

### *Glutamate*

Glutamate is synthesized within axon terminals from the amino acid glutamine. The enzyme glutaminase converts the amino acid glutamine to glutamate (**Figure 3.10**). After synthesis, vesicular transporters carry glutamate into synaptic vesicles, where it resides for later release into the synapse. Glutamate is released from *pyramidal neurons*, so named for the pyramid shape of the soma. The cerebral cortex is rich in pyramidal neurons, and the groupings of pyramidal neurons partly define different layers of the cerebral cortex.

Within the synaptic cleft, glutamate binds to any of four types of receptors (**Table 3.3**). Three of these receptors—NMDA, AMPA, and kainate receptors—are ionotropic. The fourth receptor type, the mGlu receptor, is metabotropic.

When activated, the ionotropic NMDA, AMPA, and kainate receptors allow positively charged ions, such as calcium ($Ca^{2+}$) and $Na^{+}$, to enter a neuron (**Figure 3.11**). The influx of positively charged ions can cause excitatory postsynaptic potentials. The names for these receptors come from the chemical substances used to discover them. NMDA stands for N-methyl-D-aspartate, an amino acid chemically similar to glutamate that binds to and activates these receptors. AMPA stands for α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid, a chemical used to discover this receptor. Finally, the kainate receptor is named from the chemical kainic acid.

The subtypes of mGlu receptors are groups I, II, and III receptors. Group I mGlu receptors enhance neuronal activity by activating a G protein, which leads to a cascade of other effects. However, mGlu II and III receptors differ from other

**FIGURE 3.10 Glutamate Neurotransmitter Synthesis**

Glutamate is synthesized from glutamine using the enzyme glutaminase.

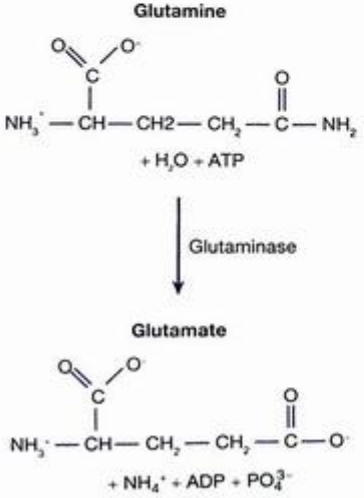
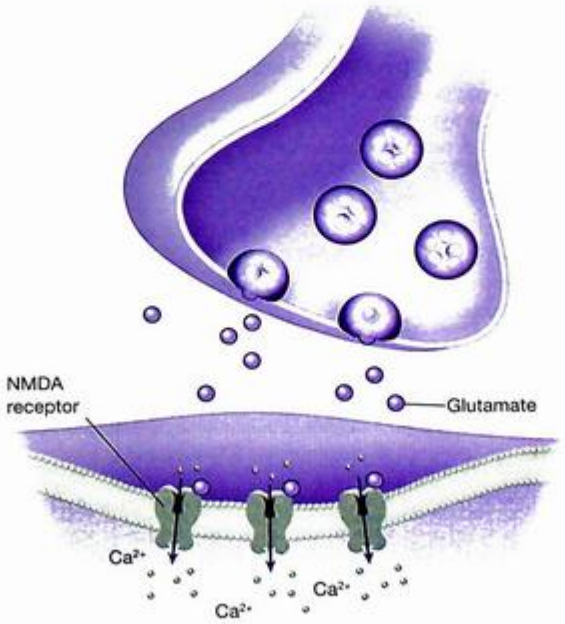


**TABLE 3.3 Glutamate Receptors**

| Receptor | Type | Effect on Neuron |
|---|---|---|
| NMDA | Ionotropic | Excitatory |
| AMPA | Ionotropic | Excitatory |
| Kainate | Ionotropic | Excitatory |
| mGlu group I | Metabotropic | Excitatory |
| mGlu group II | Metabotropic | Inhibitory |
| mGlu group III | Metabotropic | Inhibitory |

**FIGURE 3.11 Glutamate NMDA Receptor**

The glutamate NMDA receptor produces excitatory effects by allowing positively charged ions to enter a neuron.



glutamate receptors by activating a G protein that diminishes further signalling inside the neuron (Ferraguti & Shigemoto, 2006).

Glutamate receptors are found not only on neurons but also on glial cells. On astrocytes near the synaptic cleft at glutamate synapses, we find both AMPA receptors and mGlu receptors. Glutamate released from axon terminals, therefore, binds to these receptors on astrocytes as well as to receptors found on neuron terminals.

Activating glutamate receptors on astrocytes results in the $Ca^{2+}$ entering the astrocyte (Shelton & McCarthy, 1999). The influx and buildup of $Ca^{2+}$ leads to processes occurring inside astrocytes, which may include the release of glutamate from astrocytes (Parpura et al., 1994). In these cases, glutamate released from astrocytes binds to glutamate receptors found on neuron terminals (either presynaptic or postsynaptic) in the synaptic cleft, thus having a direct influence on neurotransmission (Auld & Robitaille, 2003).

After glutamate has been released from a receptor, it is removed from the synaptic cleft through any of several *excitatory amino acid transporters*. These transporters for glutamate are found on the axon terminal that released glutamate, effectively recycling glutamate for release at a later time. Astrocytes near the synaptic cleft also have excitatory amino acid transporters. Within an astrocyte, glutamate is broken down by the enzyme glutamine synthetase into the amino acid glutamine. The astrocyte then releases glutamine near the axon terminal, where it can be brought into the terminal through glutamine transporters and then used for glutamate synthesis.

*GABA.* We find the inhibitory amino acid GABA (again, the full name is γ-aminobutyric acid) in most nervous system structures. GABA, like other neurotransmitters, is synthesized from an amino acid by an enzyme. GABA is converted from the amino acid glutamate with the enzyme glutamic acid decarboxylase (GAD; also referred to as *glutamate* decarboxylase). After synthesis, vesicular transporters bring GABA neurotransmitters into synaptic vesicles (**Figure 3.12**). The drug gabapentin (Neurontin) enhances GABA neurotransmission, in part, by increasing the availability of glutamic acid decarboxylase, resulting in greater production of GABA.

There are two GABA receptors, named $GABA_A$ and $GABA_B$ (**Table 3.4**). The $GABA_A$ receptor is ionotropic, whereas the $GABA_B$ receptor is metabotropic. Both receptors produce inhibitory effects when activated by GABA. Of these two receptors, the $GABA_A$ receptor has been the most studied and is responsible for the effects of many central nervous system depressants, such as alcohol (ethanol), barbiturates, and benzodiazepines.

## Drug Profile: gabapentin

*Drug Profile features provide a brief overview of a compound discussed in the text.*

| Brand name | *Neurontin* |
|---|---|
| Mechanism of action | Increases availability of the enzyme glutamic acid decarboxlyase, which converts glutamate to GABA |
| Uses | Used for the treatment of pain, convulsions, restless leg syndrome, fibromyalgia, and anxiety |
| Similar drugs | Pregabalin (Lyrica) |

**FIGURE 3.12 GABA Neurotransmitter Synthesis**

The enzyme glutamic acid decarboxylase converts glutamate to GABA by removing the carboxylate group (circled with a dashed line) from glutamate.

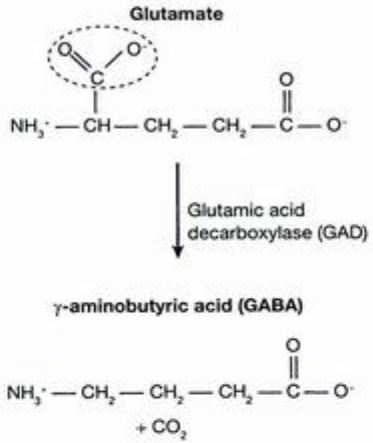



**TABLE 3.1 GABA Receptors**

| Receptor | Type | Effect on Neuron |
|---|---|---|
| $GABA_A$ | Ionotropic | Inhibitory |
| $GABA_B$ | Metabotropic | Inhibitory |

Figure 3.8 shows the ionotropic $GABA_A$ receptor. The $GABA_A$ channel contains a site for $GABA_A$, which opens when GABA binds to this site. Once the channel is open, negatively charged chloride ($Cl^-$) ions enter the neuron, resulting in IPSPs. As previously described, IPSPs cause hyperpolarization to local potentials, reducing the likelihood of action potentials.

After GABA neurotransmitters release from receptors, astrocytes terminate neurotransmission by transporting GABA into astrocytes. Within an astrocyte, the enzyme GABA aminotransferase breaks GABA down to glutamate. In some situations, enzymes further break glutamate down into glutamine, which may be released near GABA neurons and then can be used for the synthesis of GABA.

## STOP & CHECK

1. Glutamate is the most common excitatory neurotransmitter in the nervous system, whereas _____ is the most common inhibitory neurotransmitter in the nervous system.
2. Glutamate is synthesized and released from _____ neurons.
3. Of the two types of GABA receptors, the $GABA_A$ receptor is ionotropic, whereas the $GABA_B$ receptor is _____.
4. The inhibitory effects of GABA that occur at $GABA_A$ receptors result from the influx of _____ charged ions such as chloride.

1. GABA 2. pyramidal 3. metabotropic 4. negatively

## Monoamine Neurotransmitters: Dopamine, Norepinephrine, Epinephrine, and Serotonin

Chances are that you have already learned something about the neurotransmitters serotonin, dopamine, or norepinephrine in other college courses. Selective serotonin reuptake inhibitors (SSRIs), such as Prozac, for example, treat depression by increasing serotonin levels in synapses. The dopamine system plays an important role in rewarding the effects of recreational drugs and in the symptoms of schizophrenia. These neurotransmitters belong to the *monoamine* class of neurotransmitters, which includes two subgroups: the catecholamines and the indoleamines.

The catecholamines include the neurotransmitters dopamine, norepinephrine, and epinephrine. These neurotransmitters share a catechol chemical structure and have a single amine chemical group (**Figure 3.13**). The same synthesis process produces these neurotransmitters, as shown in **Figure 3.14**. This synthesis pathway begins with the essential amino acid phenylalanine.

### *Dopamine*

Dopamine is the first monoamine neurotransmitter synthesized in this process. The enzyme phenylalanine hydroxylase converts phenylalanine to the amino acid

**FIGURE 3.13 Chemical Structures for Monoamines**

Every monoamine neurotransmitter has a single amine group in its structure. The catecholamines—including dopamine, norepinephrine, and epinephrine—have a catechol nucleus in their structures.

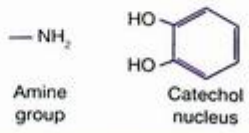
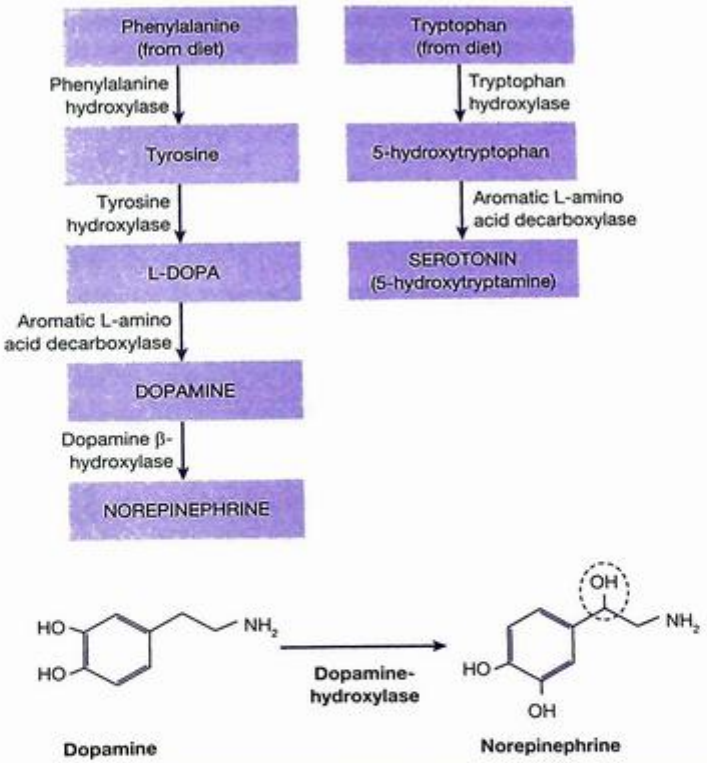


**FIGURE 3.11 Synthesis of Monoamine Neurotransmitters**

Monoamine neurotransmitters are synthesized through a series of steps beginning with an amino acid. *Inset*: Dopamine-β-hydroxylase converts dopamine to norepinephrine by adding a hydroxyl group (circled) to dopamine's structure.




tyrosine, a nonessential amino acid. Yet, tyrosine also comes from dietary sources. In particular, high-protein foods such as meats, soy, and dairy products contain large amounts of tyrosine (Figure 3.14).

The enzyme tyrosine hydroxylase converts tyrosine to L-3,4-dihydroxyphenylalanine (abbreviated as L-DOPA). The enzyme aromatic L-amino acid decarboxylase then produces dopamine from L-DOPA. In the many synthesis steps for dopamine, tyrosine hydroxylase serves as the **rate-limiting step** because it has the slowest conversion rate. Increasing tyrosine levels is not an effective means of increasing dopamine levels because the relatively slower conversion rate of tyrosine hydroxylase acts as a bottleneck for this synthesis pathway. However, increasing L-DOPA

**Rate-limiting step**
Slowest conversion rate in a synthesis process

levels will increase dopamine levels because the conversion of L-DOPA to dopamine does not depend on tyrosine hydroxylase. After synthesis, vesicular monoamine transporters (VMATs) deliver dopamine into vesicles for storage.

When prescribed as a drug, we refer to L-DOPA by its generic drug name *levodopa*. Unlike dopamine, levodopa crosses the blood–brain barrier, making this a medication capable of increasing dopamine release in the brain. As such, levodopa remains a primary medication for Parkinson's disease. The symptoms of Parkinson's disease arise from the destruction of dopamine neurons. Levodopa helps to compensate, at least temporarily, for the loss of dopamine by causing remaining dopamine neurons to produce more dopamine through steps in neurotransmitter synthesis shown in Figure 3.14.

## Drug Profile: levodopa

| | |
|---|---|
| Generic name | Levodopa |
| Mechanism of action | As a monoamine precursor, serves to increase dopamine synthesis |
| Uses | Treats Parkinson's disease by counteracting dopamine depletion caused by destroyed dopamine neurons |

Once released from an axon terminal, dopamine may bind to any of several types of *dopamine receptors* that are classified by two families: the $D_1$ receptor family and the $D_2$ receptor family (**Table 3.5**). The $D_1$ receptor family contains the $D_1$ and $D_5$ receptors, and the $D_2$ receptor family contains the $D_2$, $D_3$, and $D_4$ receptors. All dopamine receptors are metabotropic, G protein-coupled receptors. The $D_1$ family of receptors tends to have excitatory effects on neurons, whereas the $D_2$ family of receptors has inhibitory effects on neurons.

**TABLE 3.5 Dopamine Receptors**

| Receptor | Type | Effect on Neuron |
|---|---|---|
| $D_1$ | Metabotropic | Excitatory |
| $D_2$ | Metabotropic | Inhibitory |
| $D_3$ | Metabotropic | Inhibitory |
| $D_4$ | Metabotropic | Inhibitory |
| $D_5$ | Metabotropic | Excitatory |

Once dopamine releases from a dopamine receptor in the synaptic cleft, termination of dopamine transmission occurs in one of two ways. First, dopamine may be catabolized by an enzyme. One type of catabolic enzyme is **monoamine oxidase (MAO)**, which has two types—$MAO_A$ and $MAO_B$—and is located within the presynaptic neuron. Both types of MAO are capable of breaking down dopamine, as well as norepinephrine and serotonin. Another type of catabolic enzyme is **catechol-O-methyltransferase (COMT)**, which is found on the membrane of the postsynaptic terminal (Karhunen, Tilgmann, Ulmanen, & Panula, 1995). COMT catabolizes catecholamine neurotransmitters, including dopamine, norepinephrine, and epinephrine. Second, dopamine transporters also terminate dopamine neurotransmission by reuptake. After dopamine molecules pass through this transporter, vesicles store dopamine for later release.

Two brain stem structures—the *ventral tegmental area* and the *substantia nigra*—and the hypothalamus contain most of the brain's dopamine neuron cell bodies (**Figure 3.15**). Bundles of dopamine axons from these structures terminate in other parts of the brain. The dopamine pathways most important for psychoactive drugs are the mesolimbic, mesocortical, nigrostriatal, and tubero-infundibular dopamine pathways.

The **mesolimbic** and **mesocortical dopamine pathways** originate in the ventral tegmental area. The axons in the mesolimbic pathways terminate in the nucleus accumbens as well as other limbic system structures, including the amygdala and

**Monoamine oxidase (MAO)**
Enzyme that breaks down dopamine, norepinephrine, and serotonin

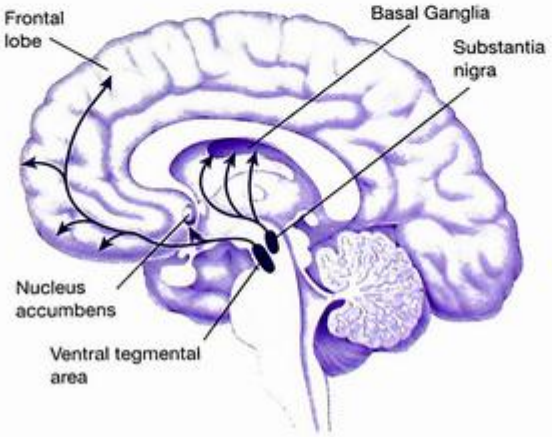
**Catechol-O-methyltransferase (COMT)**
Enzyme that breaks down dopamine and norepinephrine

**Mesolimbic dopamine pathway**
Dopamine neurons with somas in the ventral tegmental area and axons terminating in the limbic system

**Mesocortical dopamine pathway**
Set of dopamine neurons with somas in the ventral tegmental area and axons terminating in the cerebral cortex, particularly the prefrontal cortex

**FIGURE 3.15 Dopamine Neurotransmitter System**

The mesolimbic and mesocortical dopamine pathways, which originate in the ventral tegmental area; the nigrostriatal dopamine pathway, which originates in the substantia nigra; and the tubero-infundibular dopamine pathway, which originates in the hypothalamus.



**Nigrostriatal dopamine pathway**
Set of dopamine neurons with somas in the substantia nigra and axons terminating in the basal ganglia

**Tubero-infundibular dopamine pathway**
Set of dopamine neurons with somas in the hypothalamus and axons terminating in the pituitary gland, where it plays an important role in the secretion of prolactin

**Noradrenergic neurons**
Neurons that synthesize and release norepinephrine

hippocampus. The axons in the mesocortical pathways terminate in the frontal cortex, particularly the prefrontal cortex. The **nigrostriatal dopamine pathway** originates in the substantia nigra and terminates in the basal ganglia. These are the dopamine neurons linked to Parkinson's disease, as noted earlier.

The **tubero-infundibular dopamine pathway** originates in the hypothalamus and terminates in the pituitary gland. This pathway plays a role in the secretion of *prolactin*, an important hormone for maternal behavior, from the pituitary gland. In the peripheral nervous system, dopamine activates dopamine receptors found in the heart and certain arteries that enhance blood flow from increased cardiac output and dilated arteries.

### *Norepinephrine and Epinephrine*

Norepinephrine represents the next step in the catecholamine synthesis process. Further synthesis leads to epinephrine (Figure 3.14). Epinephrine shares the functions of norepinephrine in the brain but has little unique impact on brain function or psychoactive drug actions of its own. Given this, epinephrine is not discussed very often in this book.

Outside of the nervous system, norepinephrine is also known as *noradrenaline*. Thus, the term *norepinephrine* refers to its role as a neurotransmitter, whereas the term *noradrenaline* refers to its role as a hormone. Complicating things further, we use the term *noradrenaline* as the basis for the names of neurons and receptors for norepinephrine. As a result, we call a norepinephrine-releasing neuron a **noradrenergic neuron** and we call receptors for norepinephrine *adrenoceptors*.

Within noradrenergic neurons, the enzyme dopamine β-hydroxylase converts dopamine to norepinephrine (Figure 3.14). Like dopamine, vesicular monoamine transporters bring norepinephrine into synaptic vesicles for storage. After release from noradrenergic axon terminals, norepinephrine binds to adrenoceptors, which consist of both α and β types (**Table 3.6**). Both types of adrenoceptors are metabotropic receptors. The α adrenoreceptors have two subtypes: $\alpha_1$ and $\alpha_2$. The β adrenoceptors have three subtypes: $\beta_1$, $\beta_2$, and $\beta_3$. Depending on the specific receptor, activation of adrenoceptors produces either inhibitory or excitatory effects.

**TABLE 3.6** **Noradrenergic Receptors (for the Neurotransmitter Norepinephrine)**

| Receptor | Type | Effect on Neuron |
|---|---|---|
| $\alpha_1$ | Metabotropic | Excitatory |
| $\alpha_2$ | Metabotropic | Inhibitory |
| $\beta_1$ | Metabotropic | Excitatory |
| $\beta_2$ | Metabotropic | Excitatory |
| $\beta_3$ | Metabotropic | Excitatory |

Like dopamine, norepinephrine neurotransmission is terminated by the catabolic enzymes MAO or COMT or through reuptake into the axon terminal. Reuptake occurs through the *norepinephrine transporter*. We find noradrenergic neurons in the *locus coeruleus*, a structure located in the brain stem near dopamine-containing structures. Noradrenergic pathways innervate many structures throughout the brain, including the cerebral cortex, hippocampus, and amygdala (**Figure 3.16**). In the peripheral nervous system, norepinephrine activates cells in the sympathetic nervous system.

### *Serotonin*

Serotonin is part of the indoleamine class of monoamines (Table 3.2). Serotonin is also known as *5-hydroxytryptamine*, or *5-HT* for short. Given that serotonin belongs to a different category of monoamines, serotonin's synthesis pathway differs from the catecholamines. The synthesis of serotonin begins with the essential amino acid tryptophan. The enzyme tryptophan hydroxylase converts tryptophan to 5-hydroxytryptophan. From here, the enzyme aromatic L-amino acid decarboxylase—the same enzyme that converts L-DOPA to dopamine—converts 5-hydroxytryptophan to 5-hydroxytryptamine (Figure 3.14).

Once synthesized in neurons, vesicular monoamine transporters (specifically, the $VMAT_2$ transporter—the same vesicular transporters for dopamine and

**FIGURE 3.16** **Norepinephrine Neurotransmitter System**

The cell bodies for norepinephrine are mostly found in the locus coeruleus, and axons from these neurons are sent to many areas throughout the brain, including the cortex, amygdala, and structures in the hindbrain.

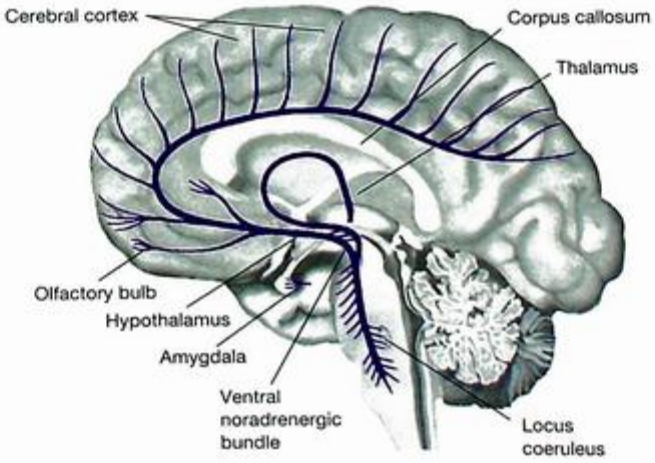


**TABLE 3.7** **5-HT Receptors (for the Neurotransmitter Serotonin, Abbreviated as "5-HT")**

| Receptor | Type | Effect on Neuron |
|---|---|---|
| $5\text{-HT}_1$ | Metabotropic | Inhibitory |
| $5\text{-HT}_2$ | Metabotropic | Excitatory |
| $5\text{-HT}_3$ | Ionotropic | Excitatory |
| $5\text{-HT}_4$ | Metabotropic | Excitatory |
| $5\text{-HT}_5$ | Metabotropic | Inhibitory |
| $5\text{-HT}_6$ | Metabotropic | Excitatory |
| $5\text{-HT}_7$ | Metabotropic | Excitatory |

norepinephrine) bring serotonin into synaptic vesicles. The major types of serotonin receptors include $5\text{-HT}_1$ through $5\text{-HT}_7$. Each receptor type includes multiple subtypes (e.g., $5\text{-HT}_{1A}$, $5\text{-HT}_{2A}$, $5\text{-HT}_{2C}$, etc.) (**Table 3.7**).

Outside the brain, the major source of serotonin comes from *enterochromaffin cells*, which line the intestinal tract (Gershon, 2013). Gut bacteria signal enterochromaffin cells to produce serotonin, and gut bacteria also synthesize tryptophan, providing enterochromaffin cells within another source, in addition to diet, of this precursor for serotonin synthesis. Tryptophan diffused into the circulatory system crosses the blood–brain barrier and becomes available for use by neurons for serotonin synthesis. Like L-DOPA for dopamine, greater levels of brain tryptophan lead to a larger production of serotonin. In this way, gut bacteria play a role in serotonin neurotransmission in the brain (Sampson & Mazmanian, 2015). In the gut, serotonin regulates some aspects of motility—the mixing and movement of material through the gastrointestinal system (Gershon, 2013).

The termination mechanisms for serotonin include enzymatic breakdown and reuptake. Like dopamine and norepinephrine, the enzyme MAO catabolizes serotonin. Otherwise, serotonin neurotransmitters are brought back into the axon terminal through reuptake via the *serotonin transporter*. Like dopamine and norepinephrine, serotonin is then stored in vesicles for later release.

The cell bodies for serotonergic neurons are located in the raphe nuclei, which are found in the brain stem near structures for dopaminergic and noradrenergic neurons. Serotonin pathways terminate in structures throughout the brain.

## STOP & CHECK

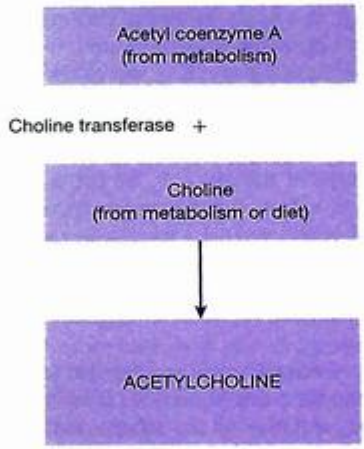
1. The monoamines include the neurotransmitters dopamine, _____, epinephrine, and serotonin.
2. How might one's diet influence dopamine neurotransmission?

3. In addition to diet, what is another source of tryptophan for the synthesis of serotonin by neurons?
4. Unlike dopamine and norepinephrine, serotonin can only be broken down by the enzyme _____.

1. norepinephrine 2. A poor diet reduces the availability of amino acids important for dopamine synthesis. For example, a protein-impoverished diet reduces tyrosine levels in the body, in turn reducing the amount of dopamine synthesized. 3. Tryptophan produced from gut bacteria. 4. MAO

**FIGURE 3.17 Acetylcholine Synthesis**

Acetylcholine is synthesized from acetyl coenzyme A and choline with the enzyme choline acetyltransferase.




## Acetylcholine

Acetylcholine is listed alone in Table 3.2 for neurotransmitters. Acetylcholine is derived from a single synthesis step by assembling *choline* and *acetyl* coenzyme A using the enzyme *choline acetyltransferase* (**Figure 3.17**). Acetylcholine neurons are referred to as **cholinergic neurons**, owing to choline's role in acetylcholine synthesis. After synthesis, the *vesicular acetylcholine transporter* brings acetylcholine into synaptic vesicles.

**Cholinergic neurons** Neurons that synthesize and release acetylcholine

The receptors for acetylcholine, called *cholinergic receptors*, have two major classes: *nicotinic receptors* and *muscarinic receptors* (**Table 3.8**). The receptor names come from compounds used to discover them. Nicotine selectively acts on

**TABLE 3.8 Cholinergic Receptors (for the Neurotransmitter Acetylcholine)**

| Receptor | Type | Effect on Neuron |
|---|---|---|
| Muscarinic $M_1$ | Metabotropic | Excitatory |
| Muscarinic $M_2$ | Metabotropic | Inhibitory |
| Muscarinic $M_3$ | Metabotropic | Excitatory |
| Muscarinic $M_4$ | Metabotropic | Inhibitory |
| Muscarinic $M_5$ | Metabotropic | Excitatory |
| Nicotinic | Ionotropic | Excitatory |

nicotinic receptors. Similarly, muscarine, a toxin found in the mushroom *Amanita muscaria*, was found to act on a separate class of cholinergic receptors.

Nicotinic receptors are ionotropic; when activated, they cause the influx of positively charged sodium ($Na^+$), potassium ($K^+$), and calcium ($Ca^{2+}$) ions. Five subunit structures make up nicotinic receptors. The names of the primary subunits are the Greek letters α and β. Other subunits include δ and ε. Each subunit has multiple subtypes, which are described by placing a numbered subscript after the subunit name. For example, one type of subunit is $\alpha_4$. So far, researchers have discovered nine α subunits ($\alpha_2$ through $\alpha_{10}$) and four β subunits ($\beta_1$ through $\beta_4$).

The configuration of nicotinic receptor subunits serves as the receptor's subtype. For example, the receptor composed of $\alpha_4$ and $\beta_2$ subunits is called the $\alpha_4\beta_2$ *nicotinic receptor*, whereas the receptor comprising only $\alpha_7$ subunits is called the $\alpha_7$ *nicotinic receptor*. Numerous nicotinic receptor subtypes are based on different subunit configurations.

Muscarinic receptors are metabotropic and coupled to G proteins. There are two families of muscarinic receptors: the $M_1$ and $M_2$ families. The subtypes of the $M_1$ receptor family are $M_1$, $M_3$, and $M_5$, and the subtypes of the $M_2$ receptor family are $M_2$ and $M_4$. In general, activation of $M_1$ family receptors produces excitatory effects within a neuron by activating second messengers. Activation of $M_2$ family receptors produces inhibitory effects within a neuron through intracellular signalling.

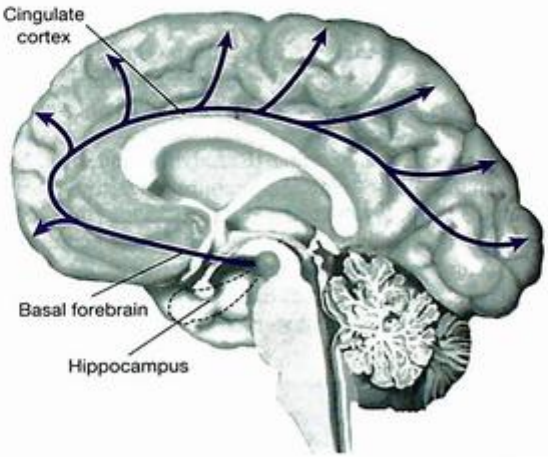
**Acetylcholinesterase** Enzyme that catabolizes, or breaks down, acetylcholine

Once released from the receptor, the enzyme **acetylcholinesterase** breaks acetylcholine down into choline and acetic acid. There is no reuptake transporter for acetylcholine, but there is a reuptake transporter for choline. Once choline is transported via the choline transporter into the axon terminal, choline acetyltransferase enzymes facilitate the synthesis of acetylcholine.

Many structures in the brain contain cholinergic neurons, including the *nucleus basalis magnocellularis*, pons, hippocampus, and tegmentum. Cholinergic axons from the nucleus basalis magnocellularis innervate the cerebral cortex. Cholinergic axons from the pons also innervate the cerebral cortex as well as the thalamus. Most cholinergic axons from hippocampal neurons remain in the hippocampus, and tegmental cholinergic axons innervate other brain stem structures, including the dopamine-rich substantia nigra and ventral tegmental area structures (**Figure 3.18**).

**FIGURE 3.18 Acetylcholine Neurotransmitter System**

Acetylcholine cell bodies are located in the basal forebrain, and acetylcholine is released in the cerebral cortex and hippocampus.




*Source:* Adapted from Woolf (1991).

Acetylcholine is also the key neurotransmitter released from parasympathetic nervous system neurons. Increased parasympathetic nervous system activation accounts for many of the effects of muscarine poisoning, for example, such as increased salivation, diarrhea, blurred vision (through pupil constriction), and labored breathing. Certain antidepressant drugs impair cholinergic neurotransmission in the parasympathetic nervous system, leading to dry mouth, constipation, and blurred vision (in this case, from dry eyes and pupil dilation).

The cholinergic nervous system is the target of both chemical warfare and therapeutic drugs. The chemical weapon *sarin gas* potently inhibits acetylcholinesterase, causing a massive buildup of acetylcholine. Sarin gas overactivates the parasympathetic nervous system, causing constriction of the lungs, ultimately causing suffocation. This weapon was developed in Nazi Germany in the 1930s and was used by Saddam Hussein during the Iran–Iraq War and on ethnic Kurds in northern Iraq in 1988 (Ganesan, Raza, & Vijayaraghavan, 2010). Sarin was also the agent used in the Japanese subway terrorist attacks in the 1990s and in the Syrian Arab Republic in 2013 (John et al., 2018; Yanagisawa, Morita, & Nakajima, 2006).

**Alzheimer's disease**
A progressive neurological disorder characterized by severe impairments in cognition, motivation, language production and comprehension, and mood regulation

Significantly less potent inhibitors of acetylcholinesterase provide a means to treat some forms of dementia, such as **Alzheimer's disease**—a progressive neurological disorder characterized by severe impairments in cognition, motivation, language production and comprehension, and mood regulation. Although neuronal

damage occurs throughout structures in the brain, Alzheimer's disease especially affects the basal forebrain, resulting in the degeneration of more than two-thirds of cholinergic neurons in this structure. Because of this, drug developers have targeted the destruction of cholinergic neurons for pharmacological treatment strategy. Such strategies do not cure this disease, but they can delay, to some extent, cognitive decline.

Currently, the first-line treatments for Alzheimer's disease consist of *acetylcholinesterase inhibitors*. By inhibiting acetylcholinesterase, these drugs raise acetylcholine levels, counteracting diminished acetylcholine levels from the loss of cholinergic neurons. The most commonly prescribed acetylcholinesterase inhibitors include donepezil (Aricept), galantamine (Razadyne), and rivastigmine (Exelon). As a class, acetylcholinesterase inhibitors stabilize cognitive function for as long as three to six months when given during the early stages of Alzheimer's disease. However, these medications fail to alter disease progression. Further, greater acetylcholine levels enhance parasympathetic nervous system functioning, leading to risk of nausea, diarrhea, and vomiting. These risks prevent physicians from increasing drug doses as cognitive impairment worsens during the disease's progression.

## Drug Profile: donepezil

| | |
|---|---|
| Brand name | *Aricept* |
| Mechanism of action | Acetylcholinesterase inhibitor |
| Uses | Treats Alzheimer's disease by counteracting acetylcholine depletion caused by destroyed cholinergic neurons |
| Similar compounds | Galantamine (Razadyne); rivastigmine (Exelon) |

**Review!** Within the autonomic nervous system, the parasympathetic nervous system reduces heart rate, digestion, and other autonomic functions (Chapter 2).

## Neuropeptides: A Large Class of Neurotransmitters

Neuropeptides make up a large class of neurotransmitters. Opioids are the most studied neuropeptides in psychopharmacology. The opioid system is acted on by opioid drugs such as heroin and morphine, and neurons for opioids terminate in parts of the brain stem and the limbic system. (Chapter 10 covers the opioid system as well as the use and actions of opioid drugs.) Other neuropeptides are often found in neurons that contain another neurotransmitter. For example, dopamine neurons also synthesize and release the neuropeptide neurotensin (Ervin & Nemeroff, 1988).

## STOP & CHECK

1. The receptor types for acetylcholine are muscarinic receptors, which are metabotropic, and _____, which are ionotropic.
2. Acetylcholine activity in the cortex and _____ has significant effects on cognitive function.
3. _____ neurotransmitters are often in neurons that synthesize another type of neurotransmitter.

1. nicotinic receptors 2. hippocampus 3. Neuropeptide

## Other Types of Chemical Transmission in the Nervous System

### Neurotrophins

**Neurotrophins** are a family of molecules that promote the survival and plasticity of neurons during development and in adulthood. Neurotrophins include nerve growth factor (typically abbreviated as NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3, and neurotrophin-4. Neurotrophins are synthesized after expression of a particular gene such as the BDNF gene for BDNF.

**Neurotrophins**
A family of molecules that promotes the survival and plasticity of neurons during development and in adulthood

Neurotrophins bind to receptor tyrosine kinases, the second family of metabotropic receptors mentioned earlier in this chapter. **Receptor tyrosine kinases** are not coupled to G proteins; instead, intracellular signalling relies on phosphorylation of a tyrosine kinase molecule located on the intracellular portion of the receptor. Neurotrophins bind to the "Trk" (pronounced "track") type of receptor tyrosine kinases. Trk stands for "tyrosine receptor kinase" (a slight rearrangement of the name of this receptor family), and there are three subtypes: TrkA, TrkB, and TrkC.

**Receptor tyrosine kinase**
A family of metabotropic receptors not coupled to a G protein; instead intracellular signalling relies on phosphorylation of a tyrosine kinase molecule located on the intracellular portion of the receptor

NGF binds selectively to TrkA receptors, NT-3 binds selectively to TrkC receptors, and both BDNF and neurotrophin-4 bind selectively to TrkB receptors. When a compatible neurotrophin binds to a Trk receptor, phosphorylation of the tyrosine kinase molecule subsequently leads to the activation of other protein kinases and usually then to gene activation. These effects can influence the strength of synaptic connections and may account for the long-term effects of some psychoactive drugs. For example, Trk receptor activation may facilitate hippocampal synaptic changes associated with antidepressant drug treatment (Li et al., 2008).

### Hormones

**Hormones** are signalling molecules derived from cholesterol and released from glands. They differ from neurotransmitters in several ways. First, hormones have widespread effects on target areas, whereas neurotransmitters are often released into tight synaptic junctions to carry out specific effects at postsynaptic terminals.

**Hormones**
Signalling molecules derived from cholesterol and released from glands

Second, hormones bind not only to membrane receptors but also to intracellular receptors and act as transcription factors. Neurotransmitters primarily bind to receptors located on the surface of a neuron. Third, hormones can be delivered throughout the body via the bloodstream, whereas neurotransmitters generally act on receptors in the close vicinity where the neurotransmitter was released. Neurotransmitters, however, are synthesized and released in the nervous system.

The central nervous system uses hormones to regulate the endocrine system. The hypothalamus directly controls the pituitary gland. The pituitary gland is sometimes referred to as the *master gland* because it releases a number of different hormones into the bloodstream that control the release of hormones from other endocrine system glands.

Neurons from the hypothalamus release two hormones into the pituitary gland: vasopressin and oxytocin. Through the pituitary gland, these two hormones enter the bloodstream and are delivered throughout the body. **Oxytocin** is particularly important for uterine contraction during childbirth, and it also contributes to milk letdown during breast-feeding. Oxytocin has also been studied for playing a role in social attachment, including feeling a sense of closeness with others, trust, and interpreting of emotions (Bartz et al., 2010; Kosfeld, Heinrichs, Zak, Fischbacher, & Fehr, 2005). **Vasopressin** is an antidiuretic hormone that causes the kidneys to absorb more water from the bloodstream. Alcohol suppresses vasopressin release, partly accounting for the frequent urination associated with alcohol consumption (Meier & Mendoza, 1976).

**Oxytocin**
Pituitary hormone important for uterine contraction during childbirth; also contributes to milk letdown during breast-feeding

**Vasopressin**
Antidiuretic hormone that causes the kidneys to absorb water from the bloodstream

**Melatonin**
Sleep-inducing hormone that plays an important role in circadian rhythm, our natural sleep cycle

The hypothalamus also has control over the pineal gland. The pineal gland releases melatonin, which is synthesized from serotonin. **Melatonin** is a sleep-inducing hormone that plays an important role in circadian rhythm, our natural sleep cycle (Marczynski, Yamaguchi, Ling, & Grodzinska, 1964). The sleep aid ramelteon (*Rozerum*) exerts its sleep-inducing effects by activating receptors for melatonin (Buysse, Bate, & Kirkpatrick, 2005; Miyamoto, Nishikawa, Doken, Hirai, Uchikawa, & Ohkawa, 2004).

## STOP & CHECK

1. Both NGF and BDNF are types of _____, which promote the survival and plasticity of neurons.
2. _____ receptors may account for the hippocampal plasticity changes caused by chronic antidepressant treatment.
3. In addition to neurotransmitters, the other major messaging chemicals in the body are _____.

1. neurotrophins 2. Trk 3. hormones

## From Actions to Effects: Probiotics and Mental Health

The number of bacteria in the body equals the number of human cells in the body (Sender, Fuchs, & Milo, 2016). The majority of these bacteria reside in the digestive

system, distributed in the colon and small intestine, and form a functional relationship with the body's organs. Within the intestinal system, gut bacteria influence the function of the enteric nervous system, make available precursors for neurotransmitter synthesis, and affect the activity of the vagus nerve. The impactful role that gut bacteria have on nervous system activity has led to research directions toward utilizing gut bacteria for therapies for mental health.

Researchers first exploring the potential connection between the body's bacteria and mood began with a basic step—assess behavior in mice lacking all bacteria (referred to as a *germfree* mouse). Sudo and colleagues (2004) compared germfree mice and nongermfree mice after they were enclosed in a small see-through tube for an hour, which causes behavioral and physiological stress responses. Between the groups, germfree mice exhibited greater elevations of the stress indicators corticosterone and adrenocorticotropic hormone. The researchers concluded that gut bacteria play a helpful role in the body's response to stress. In other studies, germfree mice show greater behavioral indicators of anxiety (e.g., Heijtz et al., 2011).

Studies have also evaluated the role of microbiota in those with major depressive disorder. In a study by Kelly and colleagues (2016), fecal samples were collected from patients with major depressive disorder and those without a mental disorder, and then the samples were administered to different groups of laboratory rats. The researchers reasoned that if microbiota mediated some of the effects of depression in humans, then the microbiota from depressed patients introduced to normal lab rats should induce depressive behavior. Compared to rats administered samples from those without depression, rats given samples from those with depression exhibited a lower preference for sugar water (something rats really enjoy)—this screen is thought to be analogous to the general lack of joy observed in depression in humans. This study also reported reduced diversity of microbiota in depressed patients, which is a finding shown in studies evaluating the association between microbiota diversity and depressive symptoms (Guida et al., 2018; Kelly et al., 2006; Kleiman et al., 2015).

These findings illustrate the influence of gut bacteria on mood as well as suggest potential strategies for improving mood (**Table 3.9**). Probiotics serve as one direction for utilizing bacteria to affect mood. A **probiotic** consists of live bacteria selected for beneficial physiological effects. An emerging term, first coined by Dinan, Stanton, and Cryan (2013), is a *psychobiotic*—live bacteria beneficial for mental health.

**Probiotic**
Live bacteria taken for beneficial physiological effects

In a study conducted by Messaoudi and colleagues (2011), human participants given a probiotic formulation (consisting of the bacteria Lactobacillus helveticus and Bifidobacterium longum) for a month exhibited reduced psychological distress. The researchers also gave the same treatments to lab rats and found that they exhibited reduced anxiety in behavioral models. In a different study, Pinto-Sanchez and colleagues (2017) administered the probiotic Bifidobacterium longum to patients with depression and *irritable bowel syndrome*—a disorder characterized by abdominal pain and diarrhea and/or constipation, among other symptoms. Following six weeks of probiotic administration, patients rated lower on indices of depressive symptoms and higher on sense of quality of life. Overall, a focus on the body's microbiome may lead the way toward novel treatment strategies for mental health.

**TABLE 3.9 Microbiota in Anxiety and Depression**

| Mood Disorder | General Findings |
|---|---|
| Anxiety | Germfree mice (mice lacking bacteria) exhibit increased stress and anxiety |
| Depression | Microbiota from depressed patients produces depressive-like behavior in rats. Reduced diversity of microbiota correlates with depressive symptoms. |

## STOP & CHECK

1. What is a germfree mouse, and why might they be used as study animals?
2. What is a probiotic?

1. Germfree mice lack bacteria, which are otherwise highly present in the body. Germfree mice enable researchers to better understand the role microbiota play, due to their absence, in normal physiological and behavior functions. 2. Bacteria with known beneficial properties for health.

## CHAPTER SUMMARY

Neurotransmission is a neuronal communication process that uses signalling molecules called *neurotransmitters*. Both electrical and chemical processes within a neuron facilitate neurotransmitter release. Electrical potential changes occur from the soma down to the axon terminal, causing the release of neurotransmitters.

Neurotransmission consists of several steps, including neurotransmitter synthesis, storage, release, receptor binding, and termination. Receptors are proteins activated by a matching neurotransmitter. There are two types of neurotransmitter receptors: ionotropic and metabotropic. Ionotropic receptors contain an ion channel, whereas metabotropic receptors utilize other proteins to convey effects. Neurotransmitter synthesis occurs from conversion of amino acids, produced either from the body or from diet. The two most common neurotransmitters in the brain are glutamate, an excitatory neurotransmitter, and GABA, an inhibitory neurotransmitter. Monoamine neurotransmitters include serotonin, dopamine, norepinephrine, and epinephrine. Monoamine oxidase enzymes break down all monoamine neurotransmitters, whereas COMT breaks down dopamine, norepinephrine, and epinephrine. Acetylcholine is synthesized and released from cholinergic neurons. The enzyme acetylcholinesterase breaks down acetylcholine. Neurotrophins are a family of molecules that promote the survival and plasticity of neurons during development and adulthood. The class of neurotrophins includes nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3, and neurotrophin-4. Hormones are chemical messengers derived from cholesterol and released from endocrine glands. The hypothalamus controls parts of the endocrine system through controlling the release of hormones from the pituitary gland. The hypothalamus also elicits melatonin secretion from the pineal gland.

## KEY TERMS

Neurotransmission 57
Electrical potential 58
Depolarization 58
Hyperpolarization 58
Ion channels 59
Resting potential 61
Voltage-gated ion channels 62
Sodium–potassium pump 62
Action potential 64
All-or-none law 65
Refractory period 65
Propagation of action potentials 65
Firing rate 66
Nodes of Ranvier 66
Neurotransmitters 67
Synaptic vesicle 67
Vesicular transporter 67
Exocytosis 69
Catabolism 69
Turnover of neurotransmitters 69
Reuptake 69
Receptor 70
Ligand 70
Autoreceptor 70
Heteroceptor 70
Ionotropic receptors 71
Metabotropic receptor 72
G protein 73
Effector enzymes 74
Second messenger 74
Protein kinase 74
Substrate protein 74
Essential amino acid 75
Glutamate 75
GABA 75
Rate-limiting step 81
Monoamine oxidase (MAO) 83
Catechol-O-methyltransferase (COMT) 83
Mesolimbic dopamine pathways 83
Mesocortical dopamine pathways 83
Nigrostriatal dopamine pathway 84
Tubero-infundibular dopamine pathway 84
Noradrenergic neurons 84
Cholinergic neurons 87
Acetylcholinesterase 88
Alzheimer's disease 89
Neurotrophins 91
Receptor tyrosine kinase 91
Hormones 91
Oxytocin 92
Vasopressin 92
Melatonin 92
Probiotic 93

CHAPTER 4

# Properties of Drugs

## Chapter Outline

- Pharmacokinetic Properties of Drugs
- Pharmacodynamic Properties of Drugs
- Psychoactive Drugs and Receptors
- Adaptations to Chronic Drug Use
- From Actions to Effects: Environmental Neurotoxicology

## Learning Objectives

- Identify the factors that affect drug absorption
- Explain the properties that impact a drug's bioavailability
- Examine conditions that affect the length of a drug's effects
- Assess a drug's actions on neurotransmission
- Differentiate the types of actions of drugs at receptors
- Evaluate the body's response to chronic drug use

In previous chapters, you learned about parts of the nervous system that are important for understanding drug effects. In this chapter, our attention turns to drugs themselves. We focus on how drugs move through the body and how they produce their actions.

As first noted in Chapter 1, pharmacology consists of two subfields called *pharmacokinetics* and *pharmacodynamics*. Pharmacokinetics refers to how drugs move throughout the body, and pharmacodynamics refers to how drugs cause biological changes in the body. Because the focus of this textbook is on how drugs produce

behavioral effects by acting in the brain, much of the material in this book concerns the pharmacodynamic effects of drugs.

Pharmacokinetic properties, however, have a lot to do with how people use drugs. For example, cocaine users prefer to smoke or snort the drug rather than consume it orally. These different methods of use do not change how cocaine acts in the brain, but they do determine how quickly cocaine reaches the brain. Thus, pharmacokinetic issues explain the common administration methods for cocaine.

## Pharmacokinetic Properties of Drugs

As first stated in Chapter 1, *pharmacokinetics* is the study of how drugs pass through the body. This process involves factors concerning how a drug is administered and how it is absorbed into the bloodstream, reaches different parts of the body, and is eliminated from the body. Designing drugs to pass through the body is a painstaking area of drug development. In fact, many therapeutic drugs fail in clinical testing because they inadequately reach the areas of the body necessary for the drug's actions. A treatment is useless if the drug cannot reach its site of action. This section of this chapter provides an overview of the four primary stages of a drug's pharmacokinetic properties: absorption, distribution, biotransformation (or metabolism), and elimination (**Figure 4.1**).

### Absorption

**Absorption**
Passage of a drug from the site of administration to the bloodstream

The process of **absorption** refers to the passage of a drug from the site of administration to the bloodstream. To do so, a drug must pass through different membranes such as the mucous membranes in the mouth or the walls of the intestines. The particular membrane that a drug must pass through depends on the drug's *route of administration*. **Figure 4.2** shows examples of absorption for different

**FIGURE 4.1 Pharmacokinetic Stages**

The life cycle of a drug in the body begins with the administration of the drug and its absorption into the bloodstream. After entering the bloodstream, drugs diffuse through membranes and into organs. Drugs are usually biologically transformed (metabolized) by enzymes, a process that most often occurs in the liver. Finally, any remaining drug or its metabolites are eliminated from the body.

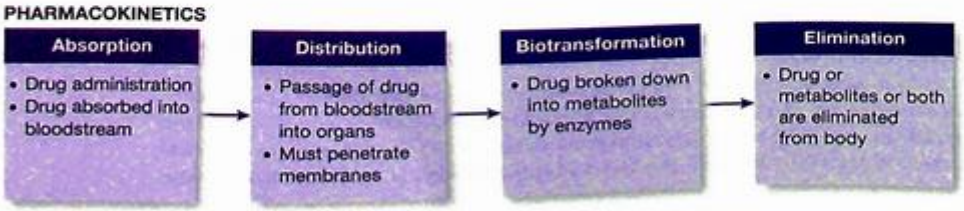
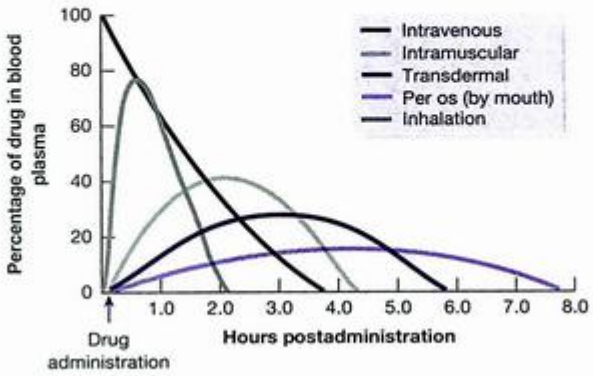


**FIGURE 4.2 Administration Routes and Speed of Drug Absorption**

The route of administration is an important determinant for how much drug reaches the bloodstream (vertical axis, shown as a percentage of drug) and the length of time needed for drug absorption (horizontal axis). This figure shows different administration routes for a fictional drug. The time needed for elimination will vary from drug to drug, but the general pattern tends to be the same.




administration routes, and **Table 4.1** describes the characteristics of different administration routes.

For the vast majority of drugs, absorption relies on a drug's ability to passively diffuse through membranes. Diffusion works best for *non-ionized* drug molecules, which have a neutral *pH* (i.e., pH = 7; recall that positively charged ions, called *bases*, have pH values above 7 and that negatively charged ions, called *acids*, have pH values below 7). Drugs have both non-ionized and ionized drug molecules produced after administration to an organism.

The ratio of non-ionized molecules to ionized molecules, which is calculated by the *Henderson-Hasselbalch equation*, depends upon the pH of the local environment and a drug's pKa. *pKa* refers to the strength of an acid; the lower the pKa value, the stronger the acid. Drugs with a pKa close to the local pH will have more non-ionized molecules than those with a pKa further away from the local pH.

For example, a drug with a pKa of 3 will have far more non-ionized molecules in the stomach, which has a pH of 1, than a drug with a pKa of 8. In this case, the drug with a pKa of 3 will have molecules that can diffuse through cell membranes lining the stomach. However, the drug with a pKa of 8 will absorb more readily in the intestines where the pH is 7 (**Figure 4.3**).

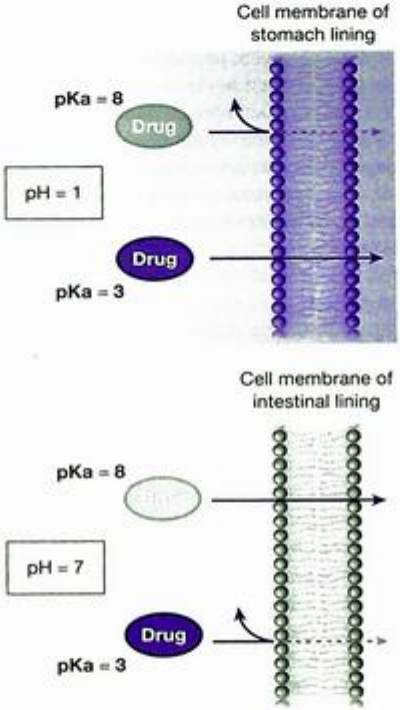
Although pKa–pH issues do affect a drug's ability to absorb into the bloodstream, the surface area of tissue matters as well. The drug with a pKa of 3 will not have many non-ionized molecules in the intestine, yet the enormous surface area of the intestines means that much of this drug will still absorb into the bloodstream. Later in this book, in Chapter 7, we consider a similar case with smoked tobacco—the pH

**TABLE 1.1 Common Routes of Administration**

| Route | Form | Absorption Amount | Time for Absorption | Other |
|---|---|---|---|---|
| Inhalation | Inhaled into lungs | High rate of absorption | Rapid | Convenient for patients and common for many drugs of abuse |
| Intramuscular | Injection into skeletal muscle | Variable, but generally more stable than oral administration | Quicker and more even than oral administration but not as rapid as intravenous injection | Not convenient for patients and not common for drug abusers |
| Intravenous | Injection into vein | 100 percent | Immediate | Unlikely for patients to administer themselves, but not uncommon for illicit drug use; drug effects occur too rapidly to counteract prescribing errors or drug overdose |
| Oral | Pill | Variable; affected by food in stomach and digestive rates | Variable, but usually at least several minutes | Convenient for patients; most preferred and common route of administration |
| Nasal and mucosal membrane | Absorbed through membranes in nasal passage or mouth | Variable but generally more stable than oral administration | Quicker and more even than oral administration but not as rapid as intravenous injection | Convenient for patients and common for drug abuse |
| Subcutaneous | Injected under skin | Variable but generally more stable than oral administration | Quicker and more even than oral administration but not as rapid as intravenous injection | Individuals can administer themselves, but not convenient to do so |
| Sublingual | Dissolved under tongue | Variable but generally more stable than oral administration | Quicker and more even than oral administration but not as rapid as intravenous injection | Can be used for individuals who may not want to take a medication (e.g., children or patients with schizophrenia) |
| Transdermal | Absorbed through skin, commonly through a skin patch | Variable but generally more stable than oral administration | Quicker and more even than oral administration but not as rapid as intravenous injection | Convenient and provides an even, sustained release of drug into bloodstream |

**FIGURE 4.3 Effects of pKa and pH on Drug Absorption**

A drug's pKa and the local pH impact a drug's ability to form non-ionized molecules, which diffuse most easily through cell membranes. The first example shows a drug with a pKa = 3 passes well through cell membranes when the local pH is 1, whereas the drug with a pKa = 8 does not. The opposite is shown below, where the local pH is 7. Thus, the closer a pKa value is to the pH, the more non-ionized molecules are formed and penetrate through cell membranes.




of the lungs is not ideal for nicotine, but the large surface area of the lungs still provides significant absorption for nicotine.

Most therapeutic drugs are orally administered. As consumers, we prefer this administration route because it is much easier than giving ourselves an injection (and less painful). After swallowing a pill or drinking a liquid, a drug passes through the stomach and into the intestines. We use the term **liberation** to describe the process of drug molecules separating from the pill or solution in which they were delivered. When a drug liberates from a pill or solution, the orally administered drug may absorb through stomach or intestinal walls as it passes through the digestive system. Generally, most drug absorption occurs in the small intestine.

**Liberation**
Process of drug molecules separating from the pill or solution in which they were delivered

The oral administration route creates a difficult challenge for drug developers, who generally aim to have drugs absorbed in the intestines. To orally administer a new drug, developers must find ways to protect the drug from digestive acids in the stomach. Encasing a drug within a tablet or capsule will manage this. At the same time, however, stomach acids must dissolve enough of the tablet or capsule to free drug molecules for absorption in the intestines. This delicate balance often reduces the amount of drug that actually reaches the bloodstream.

The duration of time needed for an orally administered drug to pass through the digestive system largely determines when drug effects occur. Although these delays also depend on unique chemical properties of the drug and the substance it is delivered in, most drugs take at least several minutes to reach the bloodstream; for intestinal absorption, it might take between 15 minutes and one hour. The *analgesic*—that is, pain-relieving—drug acetaminophen (*Tylenol*) requires about 30 minutes to provide sufficient headache relief for most people.

Users also inhale many substances, including medications such as albuterol for treating asthma or addictive substances such as tobacco. This also means that whenever you smell a chemical, the chemical is already in your body. Through the inhalation route, drugs enter the circulatory system primarily through the lungs and to some degree through membranes in the nose, mouth, and throat. Therapeutically for asthma and other lung disorders, inhalation brings a drug directly to the area needing treatment. For example, albuterol treats asthma by relaxing air passages in the lungs.

Similar to oral administration, not all of an inhaled substance absorbs through tissue to reach the bloodstream. Yet, inhaled substances absorb more quickly than orally administered drugs. For example, when tobacco is smoked, nicotine reaches the user's brain within seven seconds.

Many administration methods require an injection. Intravenous injection involves drug delivery into a vein through a hypodermic needle. This route provides for rapid drug effects and avoids absorption limitations. Intravenous injections may be used in emergency medicine if physicians need a rapid drug effect. A physician may give, for example, an intravenous injection of naloxone to a patient experiencing a heroin overdose (Sporer, 1999). Users of abused drugs may also prefer intravenous injections because of their speed of onset and full absorption of the drug.

Noncompliance to a medication provides another reason for delivering drugs by injection. These circumstances occur for some patients in psychiatric care. A patient with schizophrenia may refuse to swallow an antipsychotic medication out of suspicions about the motives of the medical care staff. To provide treatment to the patient, a nurse may provide an antipsychotic drug through an intramuscular injection in the arm or leg. To help psychiatric medical care staff with this particular patient noncompliance issue, many drug developers have pursued delivering antipsychotic drugs for sublingual administration—that is, a pill dissolves on or under the tongue—or intranasally by using a nasal spray (Miller, Ashford, Archer, Rudy, & Wermeling, 2008; Potkin, Cohen, & Panagides, 2007).

Many other administration methods for drugs exist, each differing by speed of onset and amount of absorption. Later in this section, discussion of another issue, first-pass metabolism, presents further differences between drug injection routes.

## STOP & CHECK

1. What are the four primary phases of drug pharmacokinetics?
2. The administration route for a drug is important for the _____ phase of pharmacokinetics.

1. absorption, distribution, biotransformation, and elimination 2. absorption

## Distribution

**Distribution**, the passage of a drug from the bloodstream to sites in the body, is the second stage of pharmacokinetics. After absorption of the drug into the bloodstream, the drug may need to cross certain membranes in order to reach its site of drug action. The distribution phase of pharmacokinetics affects a drug's **bioavailability**, the ability of a drug to reach a site of action. For psychoactive drugs, bioavailability depends on the drug reaching the central nervous system. To enter the brain, drugs must possess sufficient properties to permeate the blood–brain barrier.

The **blood–brain barrier** prevents substances in the blood from entering the brain by surrounding capillaries and other small vessels (**Figure 4.4**). Astrocytes form the blood–brain barrier by forcing *endothelial cells* making up capillary and vessel walls to fit tightly together (Janzer & Raff, 1987). These tight junctions prevent pathogens, hormones, and other substances from entering the brain. Nutrients and other important molecules pass through this barrier through either *passive diffusion* or *active transport*.

**Passive diffusion through the blood–brain barrier** occurs for drugs (and other substances) that possess three properties (Figure 4.4). First, drugs should be lipid (or fat) soluble, meaning that they can pass through cell membranes (Oldendorf, 1974). Second, drugs should be uncharged, which is an important reason why many neurochemicals cannot pass from the bloodstream into the brain (Butt, Jones, & Abbott, 1990). Instead, neurochemicals must be made within cells in the brain. Third, drugs should be relatively small (van de Waterbeemd, Camenisch, Folkers, Chretien, & Raevsky, 1998).

Many nutrients needed for cells in the brain lack the necessary properties for passive diffusion. Instead, nutrients enter the brain through active transport. Mechanisms for **active transport through the blood–brain barrier** consist of membrane channels or transporters that facilitate passage of chemicals through endothelial cell membranes (Figure 4.4). For example, the sugar glucose, which is an energy source for cells, passes through a channel in the blood–brain barrier in order to access cells within the brain. Some drugs enter the brain through active transport across the blood–brain barrier. For example, the drug gabapentin (*Neurontin*) crosses the blood–brain barrier through a transporter called large amino-acid transporter 1 (Wang & Welty, 1996). Physicians may prescribe gabapentin for the treatment of seizures or neuropathic pain.

**Distribution**
The passage of a drug from the bloodstream to sites in the body

**Bioavailability**
Ability of a drug to reach a site of action

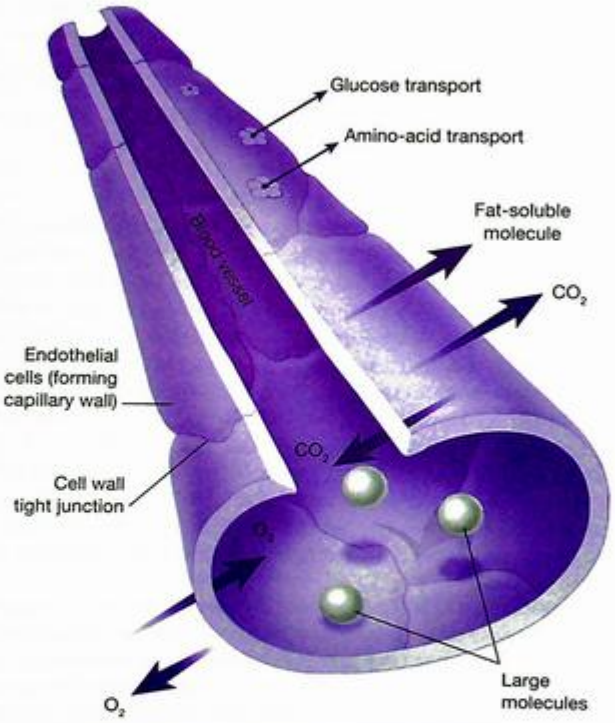
**Blood–brain barrier**
Barrier that surrounds the blood capillaries and vessels in the brain and prevents substances in the blood from entering the brain

**Passive diffusion through the blood–brain barrier**
Blood–brain barrier penetration by lipid-soluble, uncharged, small substances

**Active transport through the blood–brain barrier**
Mechanisms consisting of channels or other types of proteins that transport chemicals through endothelial cell membranes

**FIGURE 4.1 Blood–Brain Barrier**

Tight junctions between endothelial cells surrounding blood vessels in the brain prevent substances from entering the brain unless the substances possess the properties for passive diffusion or have an active transport mechanism.



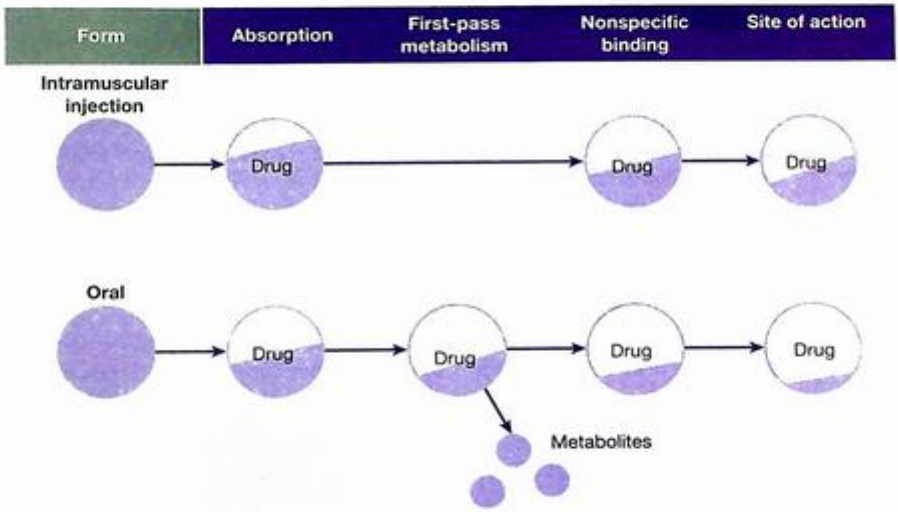

The placental barrier is also important to consider for drug effects. However, unlike with the blood–brain barrier, virtually all drugs taken by the mother can permeate the placental barrier and enter the placenta. Thus, the ease of drug permeability through this barrier may allow for harmful effects to a fetus.

**Nonspecific binding**
Binding of a drug to sites that are not the intended target for a drug's effects

Another factor for drug distribution is **nonspecific binding**, or the binding of the drug to sites that are not the intended target for drug effects (**Figure 4.5**). This may occur in the form of *protein binding*, which means that the drug binds to proteins in the bloodstream. By remaining bound to proteins in the bloodstream, drugs cannot cross the blood–brain barrier. Another form of nonspecific binding is *depot binding*, which is the binding of drugs to receptors or other parts of the body that the drug does not affect.

**FIGURE 4.5 Factors That Impact Bioavailability**

Several factors reduce the amount of drug available at the site of action. After absorption, a drug may bind to nonspecific sites in the bloodstream or body (nonspecific binding), and orally administrated drugs are susceptible to first-pass metabolism. Membrane barriers, such as the blood–brain barrier, may further reduce the amount of drug reaching the site of action.




## Biotransformation

**Biotransformation** (or **metabolism**) is the process of converting a drug into one or more other products called **metabolites.** Drugs are broken down, or catabolized, by enzymes, and this process most often takes place in the liver but may also occur in other areas such as the stomach. Biotransformation of substances may also take place within cells.

We identify two phases for biotransformation. **Phase I biotransformation** occurs first for a drug and produces a metabolite that is water soluble and easily excreted. Phase I biotransformation mostly occurs by members of the CYP-1, CYP-2, and CYP-3 cytochrome P450 enzymes. Metabolites produced in Phase I may have pharmacological properties, which we refer to as *active metabolites* (discussed later in this section).

**Phase II biotransformation** occurs from catabolism by enzymes through the process of *conjugation*, and normally occurs for metabolites produced in Phase I. Some drugs, however, may bypass Phase I biotransformation and be catabolized by Phase II biotransformation processes instead. The term *conjugation* refers to a *conjugation reaction*, involving the attachment of another molecule onto the

**Biotransformation (or metabolism)**
Process of converting a drug into one or more metabolites

**Metabolite**
Product resulting from enzymatic transformation of a drug

**Phase I biotransformation**
First biotransformation phase for a drug that normally involves P450 enzymes and produces a water-soluble metabolite

**Phase II biotransformation**
Second biotransformation phase occurring through conjugation of a drug's metabolites, making them resistant to passive diffusion

metabolite. This normally results in the metabolite becoming less able to passively diffuse through cell brains, given that the metabolites become larger, charged, and less lipid soluble.

**Review!** Catabolism refers to enzymes breaking down a substance into other molecules (Chapter 2).

Catabolic enzymes can play an important role in a person's ability to metabolize, and therefore be affected by, drugs. For example, some individuals have a poor rate of transformation for antidepressant drugs (Tiwari, Souza, & Muller, 2009). For these individuals, referred to as *poor metabolizers* in this context, the appropriate enzymes for an antidepressant drug may either be too few or, because of gene polymorphisms, have a diminished ability to transform these drugs. For poor metabolizers certain drugs remain for a longer duration in unmetabolized form, leading these individuals to have a stronger drug response than may otherwise be expected. At the same time, someone who is a *rapid metabolizer* exhibits greater levels of an enzyme or a greater ability of enzymes to metabolize antidepressant drugs. Unlike poor metabolizers, ultrarapid metabolizers tend to have a weaker drug response for certain drugs because the drug remains in the body for a shorter duration in unmetabolized form.

**Review!** A polymorphism is a difference in the encoding of a gene compared to the most common sequence in a population (Chapter 2).

Learning whether someone exhibits a difference in speed of drug metabolism can aid in prescribing drugs. For example, if an individual exhibits ultrarapid metabolism for antidepressant drugs metabolized by CYP2C19 enzymes, then a physician might prescribe an antidepressant drug not metabolized by CYP2C19 enzymes, such as fluoxetine (Prozac). Blood testing for these enzymatic activities provides an important approach for **personalized medicine**, a method of prescribing treatments most appropriate for a patient's unique biological makeup.

**Personalized medicine**
Method of prescribing treatments most appropriate for a patient's unique biological makeup

Drug biotransformation may occur before a drug circulates to the entire body, a process referred to as **first-pass metabolism** (or **first-pass effect**). First-pass metabolism occurs for drugs absorbed through the gut, which includes drugs administered orally. Drugs entering blood circulation enter the liver before being distributed to other parts of the body. Thus, liver enzymes may convert many drug molecules to metabolites before drug molecules ever enter the bloodstream (Figure 4.5). Biotransformation may also occur in the stomach, which is the case for the anti-anxiety drug (i.e., an anxiolytic) buspirone (*BuSpar*). Depending on the pill's formulation, up to approximately 90 percent of buspirone can be transformed into metabolites in the stomach after oral administration (Sakr & Andheria, 2001).

**First-pass metabolism (or first-pass effect)**
Drug metabolism that occurs prior to circulation to the body

Because of biotransformation processes, physicians treating Parkinson's disease typically administer the drug levodopa with another drug called *carbidopa*. Carbidopa prevents aromatic L-amino acid decarboxylase from converting levodopa to

dopamine while outside of the brain. Levodopa can cross the blood–brain barrier, but carbidopa and dopamine cannot. Thus, carbidopa helps keep levodopa molecules intact, allowing more of these molecules to reach the brain (Nutt, Woodward, & Anderson, 1985).

A drug's metabolites may help to explain its effects. First, metabolites may act in the body. These actions could be harmful, or they may interact with another drug a patient is taking. Second, the metabolites of a drug may offer physiological effects of their own. In this case, the metabolite is referred to as an **active metabolite**. For example, enzymes convert the antipsychotic drug quetiapine (*Seroquel*) to the metabolite N-desalkylquetiapine, which functions as an antidepressant drug (Jensen et al., 2008).

**Active metabolite**
A drug's metabolite that has physiological effects

We use the term **prodrug** to describe a compound transformed in the body to produce the active drug. Thus, the active drug in this case is actually the prodrug's active metabolite. The prodrug itself is either pharmacologically inactive or has far fewer effects than its active metabolite (Ortiz de Montellano, 2013).

**Prodrug**
A physiologically weak or inactive compound metabolized in the body to produce an active drug

Drug developers may use a prodrug as a tool for a variety of reasons, particularly for pharmacokinetic processes that may otherwise limit the bioavailability of the active drug (Rautio et al., 2008). The prodrug may bypass any absorption limitations that the active drug might have had, for example. We can also think of levodopa as a prodrug; in this case, the active "drug" is dopamine. Because dopamine cannot cross the blood–brain barrier, this limitation is overcome by using levodopa to cross the blood–brain barrier instead. The biotransformation process then takes place in dopamine neurons to produce dopamine, as previously discussed.

Third, metabolites reveal the substances a person used. Many employers require employees to undergo drug-screening tests, which detect metabolites of controlled substances. Probation programs also employ drug tests that assess metabolites as indicators of illicit substance use. For example, the opioid drug heroin will be transformed by liver enzymes to the metabolite monoacetylmorphine, although enzymes subsequently convert this enzyme to another metabolite (Rook, Hillebrand, Rosing, van Ree, & Beijnen, 2005; see Chapter 10). Drug testers may need to look for multiple metabolites to determine the actual substance taken.

## Elimination

Elimination is the last stage of pharmacokinetics. **Elimination** is the process by which a drug leaves the body. The body eliminates drugs through urine, sweat, saliva, and breath, although the particular route of elimination depends on the drug. For example, the body eliminates alcohol partly through breath. Given this, law enforcement officials use breathalyzers to determine whether an individual consumed alcohol.

**Elimination**
Process for how a drug leaves the body

**Elimination rate**
Amount of drug eliminated from the body over time

**Half-life**
Duration of time necessary for the body to eliminate half of a drug

**First-order kinetics**
The elimination of a drug in half-lives

Drugs have an **elimination rate**—that is, the amount of drug eliminated from the body over time. Physicians rely on drug elimination rates when prescribing how frequently a patient should take a medication. The elimination rate for most drugs occurs in half-lives. A **half-life** is the duration of time necessary for the body to eliminate half of a drug, usually based on a drug's concentration in blood. A drug eliminated in half-lives is referred to as having **first-order kinetics**.

**Figure 4.6** provides an illustration of a drug eliminated in half-lives. For the drug in the left panel, half of the drug leaves the body every two hours, as determined by concentration in blood plasma. The amount of drug eliminated differs for every half-life. After the first half-life shown, 2.0 milliequivalents of blood per liter (mEq/L) of drug was eliminated during the first two hours. Two hours later, 1.0 mEq/L of drug was eliminated, half of the amount of the previous half-life. Two hours after this, only 0.5 mEq/L of drug was eliminated.

However, not all drugs follow first-order kinetics for elimination. For other drugs, the elimination rate will consist of a set amount of drug per unit of time, referred to as **zero-order kinetics**. For example, the body eliminates approximately 10 to 14 milliliters (ml) of alcohol per hour. Thus, if someone ingested 20 milliliters of alcohol, the body would eliminate all of the alcohol after about two hours. The graph on the right in Figure 4.6 shows a fictional drug eliminated according to zero-order kinetics.

**Zero-order kinetics**
The elimination of a drug in non-half-lives

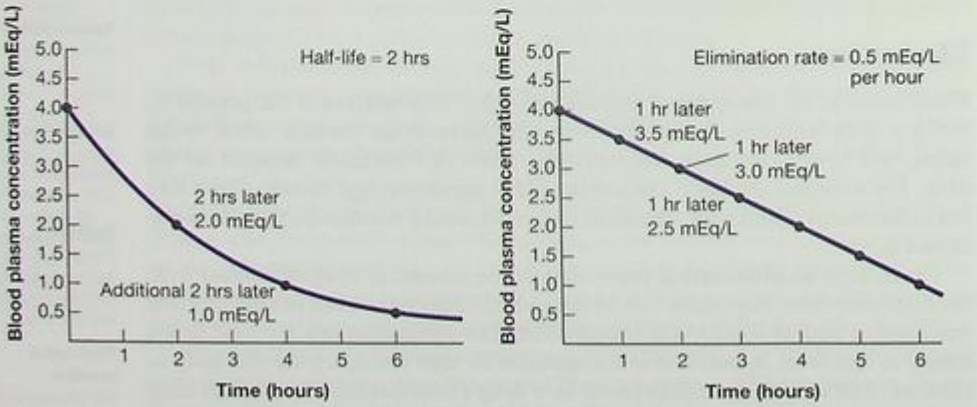
A drug's elimination rate determines how long effects will last. Physicians use elimination rate information when prescribing how frequently a patient should take a medication. In doing so, they can have patients take the next dose of medication at a time when the effects from the previous treatment begin to subside. In this way, drug effects reach a *steady state*.

**Steady state (for drug concentrations)**
A sustained concentration level of drug in the body

A **steady state (for drug concentrations)** is a sustained level of drug in the body. This is why a doctor may prescribe a drug to be taken, for example, three times a day: The drug's half-life might be about six to eight hours. Thus, as approximately half of the drug is still in the body six to eight hours later, the next administration of the drug would boost the drug concentrations back to therapeutically effective

**FIGURE 4.6** First-Order and Zero-Order Kinetics

The body eliminates drugs in half-lives (left) or as a set amount of drug per unit of time (right). For elimination according to half-lives, half of a drug is eliminated from the body per unit of time. The drug in the left panel eliminates by half every two hours. However, the drug in the right panel eliminates 0.5 millequivalents of blood per liter (mEq/L) every 30 minutes.



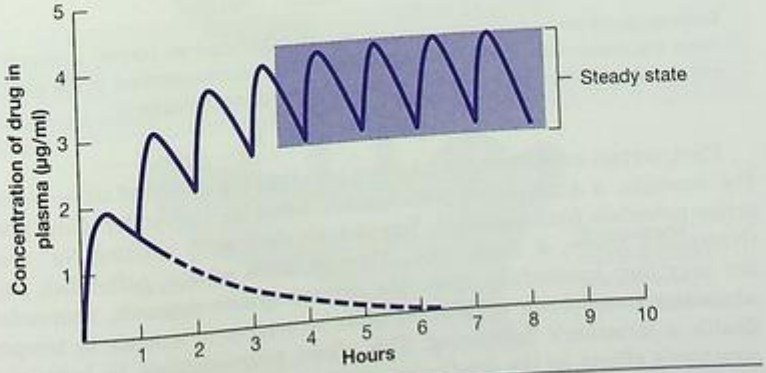
levels. **Figure 4.7** provides an illustration of a dosing schedule that achieves a steady state for drug concentration in blood.

For certain types of orally administered drugs, manufacturers may design a formulation that slowly releases the drug as it passes through the digestive system. We refer to these formulations as *modified release forms*, also called *controlled release* and *extended release*. These formulations allow taking a drug less frequently while still providing sufficient release of the drug to reach steady therapeutic levels. Thus, for example, a modified release form may require taking the drug once per day, whereas a normal formulation may require taking the drug three times per day. Modified release forms are especially useful for drugs with shorter half-lives. Given that a single oral tablet or capsule may include the equivalent of multiple doses of a drug, a modified release form contains a single large dose of the drug, but its slow release makes the absorption of the drug approximately equivalent to the drug taken as a normal formulation.

Conditions may occur that cause modified release formulations to release far more of a dose than they were designed to, a situation referred to as *dose dumping*. Dose dumping can occur when certain polymers used in modified release formulations dissolve in alcohol, causing rapid release of the drug. In 2015, the FDA pulled the extended release form of the opioid analgesic hydromorphone (*Pallodone*) due to dose dumping among patients who consumed alcohol while taking it. Among these patients, alcohol consumption led to six-fold increases of hydromorphone in blood plasma, leading to a significant risk of adverse effects (D'Souza, Mayock, & Salt, 2017).

**FIGURE 4.7** **Drug Steady State**

The half-life of a drug can be used to determine when later administrations of the drug should be given. Eventually, a steady state can develop between the rate of drug elimination from a previous administration and the rate of drug absorption from the next administration.




Source: Poling and Byrne (2000).

## STOP & CHECK

1. What is bioavailability?
2. What type of enzymes metabolize most drugs?
3. How might first-pass metabolism affect a drug's pharmacological effects?
4. Why is a steady state important for therapeutic drug effects?

1. Bioavailability describes a drug's ability to reach its site of action. 2. Cytochrome P450 enzymes 3. First-pass metabolism consists of the conversion of drug molecules to metabolites, causing less of a drug to be available for reaching its site of action. 4. As a medical treatment, sustained drug effects are usually necessary to combat a particular illness. Thus, physicians derive a treatment schedule to achieve a steady state for drug effects.

## Pharmacodynamic Properties of Drugs

*Pharmacodynamics* refers to the mechanisms of action for a drug that account for a drug's effects. For many psychoactive drugs, particularly those covered in this text, pharmacodynamics deals largely with the actions of a drug at synapses. Drugs also impact the properties governing behavior, including motivation, ability to attend to stimuli, and the effectiveness of rewards, among other effects on behavior. The effects on behavior, sometimes referred to as the *behavioral actions of drugs*, are reviewed in more detail in Chapter 5.

Depending on a drug's unique characteristics, it may alter any stage of neurotransmission. As presented in Chapter 3, neurotransmission consists of synaptic events that include action potentials reaching the axon terminal, the influx of calcium, the fusing of vesicles to membrane walls, and the emptying of stored neurotransmitters into the synaptic cleft. Within the synaptic cleft, neurotransmitters may bind to receptors. Then, neurotransmission terminates. The following paragraphs provide examples of drug actions occurring at different stages of neurotransmission.

**Review!** Termination of neurotransmission occurs when enzymes convert a neurotransmitter into metabolites, membrane transporters return neurotransmitters to the axon terminal, or transporters draw neurotransmitters into astrocytes (Chapter 3).

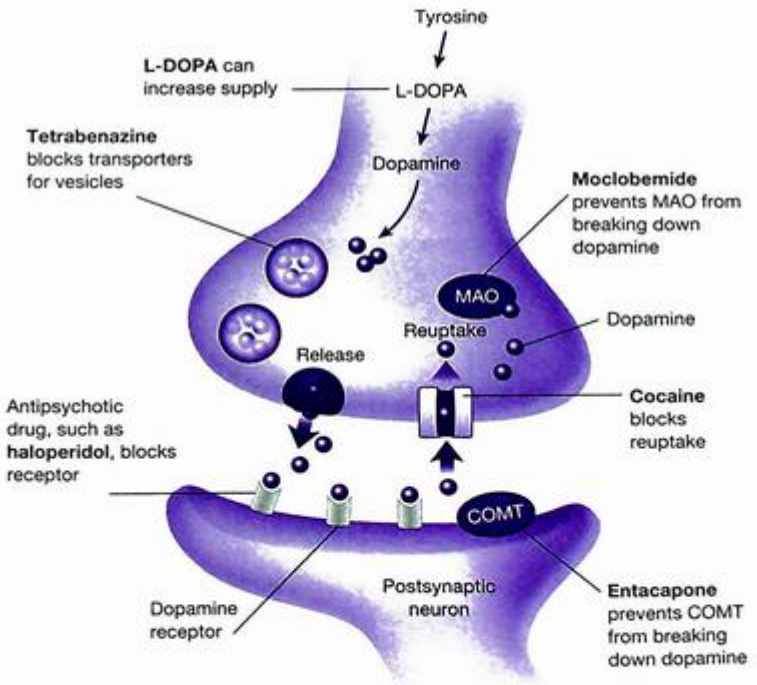
First, certain substances can interfere with the propagation of action potentials. For example, a toxin called *tetrodotoxin*, found in the puffer fish, prevents action potentials from occurring. Tetrodotoxin does so by blocking $Na^+$ channels (Narahashi, Moore, & Scott, 1964). Through these actions, puffer fish paralyze any prey they successfully inject. For nervous system research, neuroscientists administer tetrodotoxin to different brain structures in animals to temporarily disable a structure's functioning. This allows neuroscientists to learn about a structure's effects on the functioning of other structures in the brain as well as the importance a structure has for behavior.

**Review!** Action potentials consist of the rapid influx of $Na^+$ ions through open $Na^+$ channels (Chapter 3).

**Figure 4.8** provides examples of drug actions on dopamine neurotransmission. Many substances can alter the synthesis for dopamine. The precursor molecule for dopamine, L-DOPA, also serves as a drug for the treatment of Parkinson's disease (we referred to this as "levodopa" in previous chapters). By increasing the number of L-DOPA molecules within dopamine neurons, increased production of dopamine occurs.

**FIGURE 4.8 Drug Actions on Neurotransmission**

Drugs can alter any step in neurotransmission, including synthesis of a neurotransmitter, storage of a neurotransmitter, synaptic release of a neurotransmitter, enzymatic breakdown of a neurotransmitter, and reuptake of a neurotransmitter. Drugs may also act on receptors for neurotransmitters.



Drugs also may interfere with neurotransmitter storage in vesicles. The drug *tetrabenazine (Xenazine)* prevents dopamine storage by blocking transport of dopamine into vesicles. Subsequently, dopamine molecules become catabolized by enzymes leading to depletion of dopamine (Pettibone, Totaro, & Pflueger, 1984). The dopamine-depleting effects of tetrabenazine diminish the degree of writhing, facial tics, and other abnormal movements seen in Huntington's disease (Paleacu, 2007).

Drugs may also interfere with the binding of a neurotransmitter to a receptor. Figure 4.8 shows an antipsychotic drug called *haloperidol* binding to a dopamine $D_2$ receptor. Haloperidol acts through a basic receptor mechanism called *receptor antagonism* (described later in this chapter). As a receptor antagonist, haloperidol binds to the $D_2$ receptor and prevents dopamine from binding to and activating the $D_2$ receptor. Through this action, haloperidol prevents dopamine neurotransmission through the $D_2$ receptors (Seeman, Chau-Wong, Tedesco, & Wong, 1975). The next section of this chapter describes drug actions at receptors in greater detail.

Drugs can alter the activity of enzymes that break down neurotransmitters. Figure 4.8 shows a drug bound to both the monoamine oxidase (MAO) and catechol-O-methyltransferase (COMT) enzymes. For MAO, an antidepressant drug called *moclobemide* binds to and prevents MAO from breaking down dopamine (Stefanis, Alevizos, & Papadimitriou, 1982). As described in greater detail in Chapter 14, MAO inhibitors such as moclobemide may reduce depressive symptoms by enhancing neurotransmission of dopamine, as well as the neurotransmitters serotonin and norepinephrine.

Figure 4.8 also shows a drug called *entacapone* acting on the enzyme COMT. Entacapone belongs to a class of drugs called COMT inhibitors. Like MAO inhibitors, COMT inhibitors increase dopamine levels. COMT inhibitors serve as another treatment option for Parkinson's disease (Guttman et al., 1993).

Many drugs also interfere with the reuptake of neurotransmitters. Figure 4.8 shows the psychostimulant drug *cocaine* bound to the dopamine transporter. Cocaine blocks the dopamine transporter, preventing dopamine from entering the axon terminal. This action results in increased dopamine levels in the synaptic cleft and the continuation of dopamine neurotransmission.

## Drug Profile: tetrabenazine

| | |
|---|---|
| Brand name: | *Xenazine* |
| Mechanism of action | Inhibits transport of dopamine into vesicles |
| Uses | Reduces degree of abnormal movements occurring in Huntington's disease |

**Review!** The dopamine transporter sends dopamine from the synaptic cleft into a dopamine axon terminal (Chapter 3).

## STOP & CHECK

1. How might a drug, by acting on a neurotransmitter storage vesicle, diminish levels of the neurotransmitter?
2. How does a drug inhibiting the enzyme MAO increase dopamine levels?

1. As with tetrabenazine, an inability for a neuron to store a neurotransmitter leaves neurotransmitters susceptible to breakdown by enzymes. 2. MAO catabolizes, or breaks down, dopamine; thus, preventing MAO from doing so will increase dopamine levels.

## Psychoactive Drugs and Receptors

As one of the many ways that a drug can alter neurotransmission, most psychoactive drugs act on receptors for neurotransmitters. The actions of a drug at a receptor depend on how well a drug binds to the receptor and the effects a drug has on the receptor. Researchers describe these two considerations as binding affinity and receptor efficacy. **Binding affinity** refers to a drug's strength of binding to a receptor, and **receptor efficacy** refers to a drug's ability to activate a receptor.

**Binding affinity**
Drug's strength of binding to a receptor

**Receptor efficacy**
Drug's ability to alter the activity of receptor

Researchers measure a drug's binding affinity using techniques described in **Box 4.1**. These techniques result in a value for drugs called a *dissociation constant*, generally noted as $K_d$, or an inhibition constant, noted as $K_i$. These values derive from the level of drug concentration necessary to bind to receptors. For both constants, *the lower the value, the greater a drug's binding affinity.*

## BOX 4.1

### RADIOLIGAND BINDING FOR MEASURING RECEPTOR AFFINITY

*Radioligand binding* is an important technique for studying the affinity and efficacy that drugs have for receptors. The term *ligand* refers to a chemical substance that binds to a receptor, as noted in an earlier chapter. A radioligand is produced by adding a radioactive element to a ligand. As another reminder, affinity refers to a drug's strength of binding to a receptor.

Researchers conduct most radioligand experiments using dissected brain tissue that was mixed together with a chemical solution called a *buffer*, forming a homogenized solution of brain tissue and buffer. Another approach uses a large collection of cells grown in culture, referred to as *cell lines*, for radioligand experiments. After preparing the brain tissue using either method, researchers apply the radioligand to the tissue solution.

Afterward, the tissue solution, which contains both brain tissue and the radioligand, is passed through a filter. These filters allow the buffer solution to pass through but not brain tissue. After filtering, the filter contains brain tissue along with any of the radioligand bound to receptors in the brain tissue.

*(Continued)*

(Continued)

Researchers then use radioactivity counters on the filters. If the drug successfully binds to receptors in the brain tissue, then the researchers will find high radioactivity counts in the filters. However, if the radioligand bound to few receptors in the tissue, then the radioligand would have passed through the filter with the rest of the solution. In this case, researchers would detect low radioactivity counts from the filter.

**Box 4.1 Figure 1** shows an example of results from a radioligand binding experiment. This example shows, using a percentage, how many receptors the drug occupied. The *y*-axis of this graph shows the percentage of receptors occupied. The *x*-axis shows the different amounts of radioligand used, shown as the drug concentration expressed as molality. *Molality*, a term used in chemistry, refers to the number of moles (mol) per volume of solution. A *mole* refers to the number of grams of a substance divided by the molecular weight of the substance—think of this as the amount of substance.

The term called $B_{max}$, the abbreviation for *maximum binding potential*, refers to the amount of drug that fully binds to a population of receptors. In Box 4.1 Figure 1, the $B_{max}$ value of the radioligand is $10^{-3}$ moles/liter (or 0.001 moles/liter), the concentration that occupies 100 percent of the population of receptors. The $K_d$ value, or *dissociation constant*, refers to the amount of drug that occupies 50 percent of receptors. Drugs with low $K_d$ values can achieve 50 percent receptor occupancy at lower drug concentrations than drugs with higher $K_d$ values. For interpreting these data, think of it this way: the lower the $K_d$ value, the greater a drug's receptor affinity.

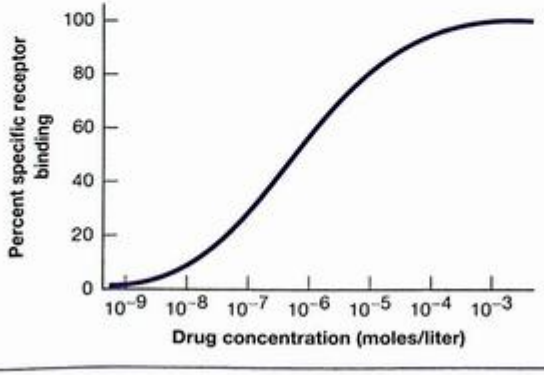
An alternative approach for assessing receptor affinities produces an inhibition constant, or $K_i$ value. This approach uses similar radioligand experimental procedures, except that $K_i$ values are derived by assessing the competition between two different drugs. Only one of the drugs serves as the radioligand; the other drug is not radioactive.

For this procedure, a researcher places both the radioligand and the nonradioactive drug into the same brain tissue solution. In this way, the researcher assesses the affinity of the nonradioactive drug by how well it binds to these receptors in the presence of the radioligand. The compound with the higher receptor affinity binds to receptors in place of the compound with the lower receptor affinity. In this case, fewer radioactivity counts indicate that the nonradioactive compound had a greater receptor affinity than the radioligand.

**Box 4.1 Figure 2** shows an example of results from a $K_i$ experiment. Like Box 4.1_Figure 1, this graph provides

## BOX 4.1 FIGURE 1 Receptor Occupancy

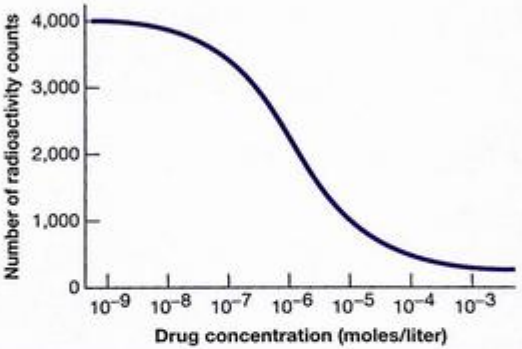
This figure shows percentage occupancy with the percentage of receptors for a population shown on the *y*-axis and the drug concentration on the *x*-axis, expressed in molality.



the concentration of a drug—in this case, the nonradioactive drug—on the *x*-axis. In this figure, however, the *y*-axis refers to the percentage of receptors bound by the radioligand. According to the figure, greater receptor occupancy by the radioligand occurred with the lowest concentration of the nonradioactive drug, whereas lower receptor occupancy by the radioligand occurred with the highest concentration of the nonradioactive drug. The $K_i$ value represents the concentration of the nonradioactive compound that caused the radioactive compound to provide 50 percent receptor occupancy. Similar to $K_d$, the lower the $K_i$ value the greater the compound's affinity (in this case, the nonradioactive drug) for the receptor.

**BOX 4.1 FIGURE 2 Receptor Binding**

This figure shows a $K_i$ experiment. The *y*-axis shows radioactivity counts, and the *x*-axis shows the concentration for the nonradioactive drug.




The previous section, which presented the different ways a drug can alter neurotransmission, used the antipsychotic drug haloperidol as an example of a drug binding to a dopamine $D_2$ receptor. **Table 4.2** shows haloperidol's binding affinity, along with related compounds, for the $D_2$ receptor as well as the binding affinity of dopamine for the $D_2$ receptor. You may be surprised to see that haloperidol has a far greater affinity for the dopamine $D_2$ receptor than dopamine does. This is another important point about drugs: They can outcompete a receptor's natural neurotransmitter.

Drugs may produce a variety of different effects on receptors through binding to a receptor's neurotransmitter site. The primary receptor actions, which may occur either for an ionotropic receptor or a metabotropic receptor, include *agonism*, *antagonism*, and *partial agonism*.[1] **Box 4.2** presents a method researchers use to determine a drug's efficacy at a metabotropic receptor. **Figure 4.9** illustrates the receptor activity taking place for a drug acting as an agonist, antagonist, or partial agonist at a metabotropic receptor. The "Before" column shows the receptor just after a drug binds to it. The "After" column illustrates the subsequent changes to the activity of the receptor's G protein.

[1]Another function is *inverse agonism*, but that is beyond the scope of this book.

**TABLE 4.2** The Dissociation Constant ($K_d$) in nM* for Dopamine and Selected Antipsychotic Drugs at the Dopamine $D_2$ Receptor

| Substance | $K_d$ (in nM) |
|---|---|
| Chlorpromazine | 4.8 |
| Haloperidol | 2.6 |
| Chlorprothixene | 8.0 |
| Dopamine | 544 |

*Source:* Richelson and Nelson (1984); Richelson and Souder (2000); Seeman (2001); and Sokoloff et al. (1992).

*n = nano, M = molality

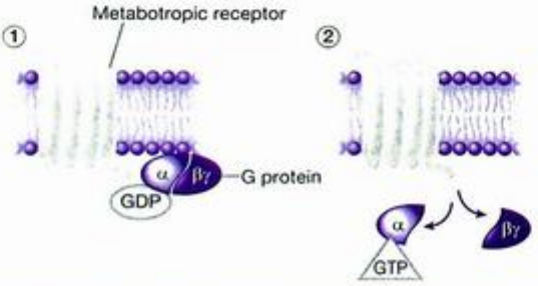
# BOX 4.2

## THE [$^{35}$S]GTPγS BINDING ASSAY ASSESSES G-PROTEIN ACTIVATION

The process of activating and deactivating G proteins depends on two biochemicals: guanosine diphosphate (GDP) and guanosine triphosphate (GTP). Before receptor activation by a neurotransmitter, GDP is bound to the inactive alpha subunit of a G protein. When a neurotransmitter or agonist activates a receptor, GTP replaces GDP on the alpha subunit, and this switch from GDP to GTP characterizes an active G-protein state (**Box 4.2 Figure 1**). This active G-protein state ends when the alpha subunit hydrolyzes GTP, causing a conversion from GTP to GDP. With GDP attached to the alpha subunit, the G protein returns to an inactive state, just as it was before the receptor was activated by a neurotransmitter.

**BOX 4.2 FIGURE 1** G-Protein Activation

During an inactive state for a G-protein coupled metabotropic receptor, GDP is bound to the G protein's α subunit (left). When an agonist activates the receptor, GTP replaces GDP on the α subunit, leading to a separation of the α subunit from the βγ subunit (right); these subunits go on to carry out intracellular signalling processes, as described in Chapter 3. GDP = guanosine diphosphate; GTP = guanosine triphosphate.



The [$^{35}$S]GTPγS binding assay employs a radioactivity compound to assess the ability of drugs to activate G proteins. Because this is a binding assay, the procedure used involves tissue and radioactivity counting procedures similar to those described in Box 4.1. [$^{35}$S]GTPγS is an analogue of GTP, and as an analogue it can replace GTP when the G protein is activated. However, unlike with GTP, researchers can measure [$^{35}$S]GTPγS using radioactivity counters. Another advantage of [$^{35}$S]GTPγS is that the alpha subunit cannot convert it into GDP. Thus, the label of an active G protein does not vanish before researchers can measure radioactivity counts.

**Box 4.2 Figure 2** shows a graph providing the ability of three drugs to bind to a receptor (left) and the ability to activate the receptor as measured using [$^{35}$S]GTPγS (right). As shown in the left graph, each drug fully occupies the population of receptors and does so at similar dosages. Yet, the [$^{35}$S]GTPγS assay demonstrates that these drugs have different abilities to activate the receptor. At high-enough concentrations, drug A exhibits full radioactivity counts, demonstrating full activation of the receptors' G proteins. Drug B achieves no more than half of drug A's radioactivity counts. Finally, drug C results in no radioactivity counts from [$^{35}$S]GTPγS.

## BOX 4.2 FIGURE 2 G-Protein Activation for Agonists, Partial Agonists, and Antagonists

The graph on the left shows the percentage of a receptor population occupied by three different drugs. The graph on the right shows the number of [$^{35}$S]GTPγS radioactivity counts. The *x*-axis for both figures refers to the concentration of drug expressed in molality (i.e., moles per liter). The illustration (right panel) reveals that drug A functions as a full agonist because it fully activates G proteins. Drug B functions as a partial agonist because, within a population of receptors, drug B fails to activate all of the G proteins. Finally, drug C acts as an antagonist—it lacks the capacity to activate receptors.

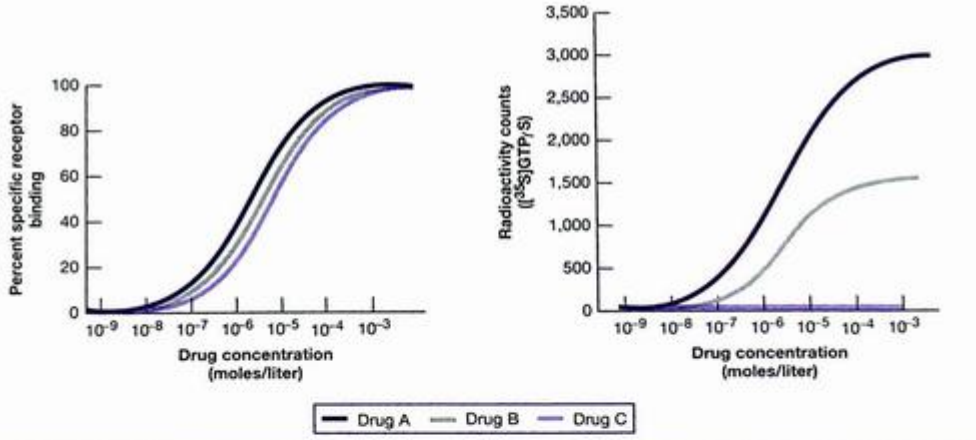
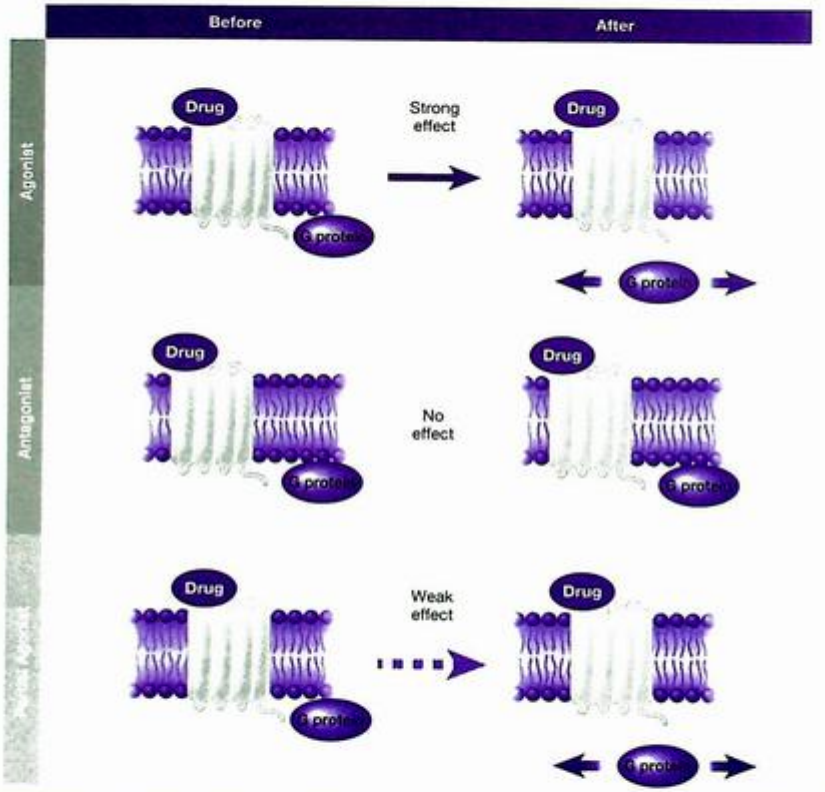


**FIGURE 4.9 Drug Actions for Metabotropic Receptors**

Drugs can have different types of action at receptors. An agonist (first row) will bind to a receptor (first column) and cause the receptor to shift into an active state (second column). The strong preference for the active state is indicated by the thick arrow. An antagonist (second row) will bind to a receptor but fail to shift the receptor's conformation into an active state (i.e., no effect). A partial agonist (third row) will bind to a receptor but is weaker, compared to an agonist, for shifting the receptor's conformation into an active state, as shown by the dashed line. The partial agonist might cause no effect for a receptor, leading it to remain in the "before" state, or it may activate it, leading it to the "after" state.




**Review!** Metabotropic receptors can cause change within neurons by activating G proteins (Chapter 3).

**Agonist**
Drug that activates a neurotransmitter receptor

An **agonist** refers to a drug that activates a neurotransmitter receptor. Researchers also refer to agonists as *full agonists* to contrast these drugs with partial agonists, described shortly. For the first line of Figure 4.9, a drug acting as an agonist

is first shown bound to the receptor with a stationary G protein adjacent to the receptor. After the agonist binds to the receptor, the G protein separates from the receptor and elicits biological actions within the neuron.

**Review!** When activated, G proteins separate into α and βγ subunits leading to activation of ion channels or enzymes (Chapter 3).

The second row of Figure 4.9 shows a drug action as an antagonist. Unlike an agonist, an **antagonist** refers to a drug that fails to activate a receptor. Thus, after an antagonist binds to a receptor, the G protein remains inactive. Antagonists for receptors may be *competitive* or *noncompetitive antagonists*. **Competitive antagonists** bind to the same site as a neurotransmitter, preventing a neurotransmitter from binding to the receptor. The second row of Figure 4.9 illustrates a competitive antagonist for the receptor. A **noncompetitive antagonist** does not bind to the same site as a neurotransmitter, but it does prevent the neurotransmitter from activating the receptor. The next figure (Figure 4.10) shows an example of a noncompetitive antagonist for an ionotropic receptor.

**Antagonist**
Drug that fails to activate a receptor and prevents a neurotransmitter from activating the receptor

**Competitive antagonist**
Drug that binds to the same site as a neurotransmitter, preventing a neurotransmitter from binding to the receptor

**Noncompetitive antagonist**
Drug that does not prevent a neurotransmitter from binding to the receptor but does prevent the neurotransmitter from activating the receptor

The third line of Figure 4.9 presents a drug acting as a **partial agonist**—that is, it possesses a weaker efficacy for activating receptors than a full agonist. These weaker effects mean that a partial agonist *may or may not* activate a receptor (conveyed by the arrow labeled "weak effect"). Thus, the G protein may separate and elicit effects within a neuron, or it may remain inactive, thereby producing no effects.

**Partial agonist**
Drug that possesses a weaker efficacy for activating receptors than a full agonist

While we're looking at an illustration of a single receptor, keep in mind that drug administration leads to a flood of drug molecules in the brain, which in turn bind to many thousands of receptors. Thus, among the entire population of receptors in the brain that the partial agonist drug binds to, a portion of the receptors will be activated while the remaining portion will not.

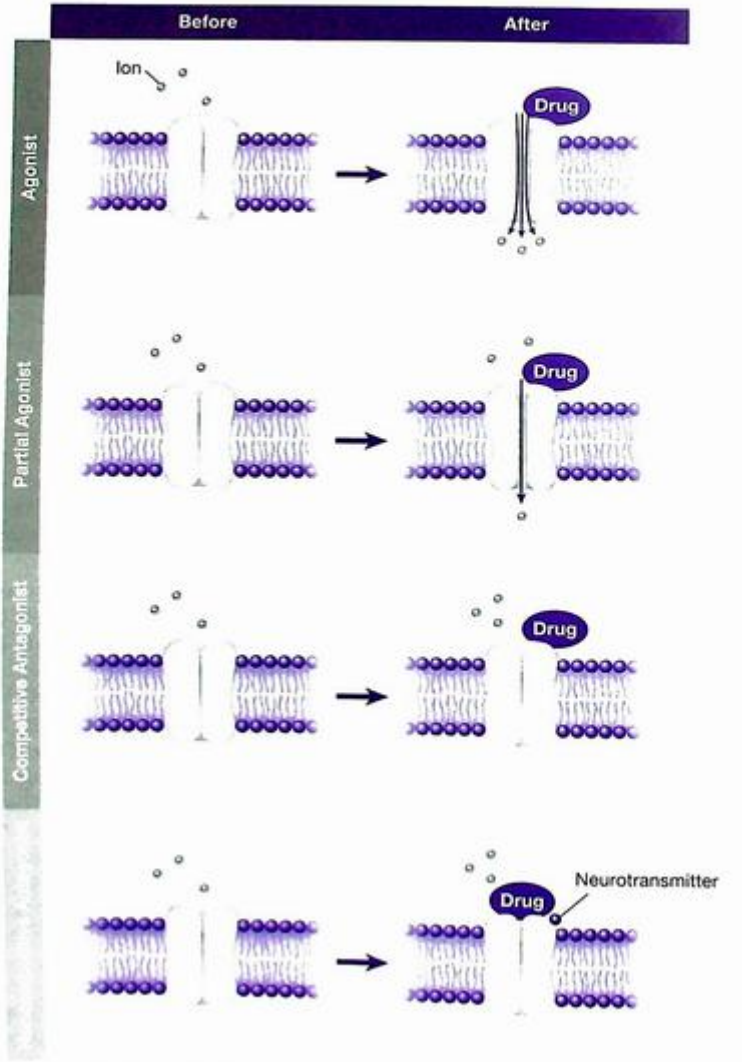
When observing the effects of a partial agonist drug, the drug will appear to have a weaker maximum effect compared to a full agonist. For example, opioid drugs suppress breathing, and for a full opioid agonist, such as fentanyl, high-enough doses can entirely cease respiration. The opioid partial agonist drug buprenorphine also suppresses breathing, but the drug reaches a ceiling effect, thus limiting the degree of respiratory depression the drug produces (Dahan et al., 2005; Dahan et al., 2006).

Although these examples concerned metabotropic receptors, similar drug effects occur at ionotropic receptors. For an ionotropic receptor, an agonist causes the attached channel to open, allowing ions to pass in or out of the neuron, as shown in the first row of **Figure 4.10**. The second row shows a partial agonist for an ionotropic receptor. In this case, a partial agonist drug partially opens the ion channel, allowing fewer ions to flow through compared to a fully open channel. For example, the compound kainate functions as a partial agonist for the glutamate AMPA receptor, because kainate causes a weaker flow of ions through the AMPA receptor channel than a full agonist produces (Arinaminpathy, Sansom, & Biggin, 2002; Armstrong & Gouaux, 2000).

The third row of Figure 4.10 shows a competitive antagonist for an ionotropic receptor, which fails to activate the receptor and prevents a neurotransmitter from

**FIGURE 4.10 Drug Actions for Ionotropic Receptors**

Although an agonist will fully activate an ionotropic receptor, causing the channel to fully open, a partial agonist will only partially open the ion channel. In these cases, more ions can flow through the fully open channel than can flow through a partially open channel. A competitive antagonist fails to activate the receptor, preventing neurotransmitters from binding to neurotransmitter sites on the receptor. A noncompetitive antagonist prevents receptor activation, but does not block a neurotransmitter from the neurotransmitter site.



binding to the receptor. For example, bicuculline acts as a competitive antagonist for $GABA_A$ ionotropic receptors. By preventing GABA-mediated inhibition of nervous system functioning, bicuculline causes greater activity in the nervous system. In fact, researchers study bicuculline-induced seizures in laboratory animals to study *epilepsy* (Johnston, 2013).

The last row of Figure 4.10 shows a noncompetitive antagonist. For this illustration, a neurotransmitter binds to the receptor, but a drug binds to a different site and prevents the neurotransmitter from activating the receptor. For example, *phencyclidine (PCP)*, a drug of abuse (discussed in Chapter 12), functions as a noncompetitive antagonist for glutamate NMDA receptors. Glutamate can bind to an NMDA receptor, but PCP prevents ions from passing through the receptor.

## Drug Profile: bicuculline

| | |
|---|---|
| Brand name | None; only used as a research compound |
| Mechanism of action | Competitive antagonist for $GABA_A$ receptors |
| Uses | Used in research to learn about GABA neurotransmission and to study seizures |

Drugs may also act as allosteric regulators. An *allosteric regulator* is a substance that binds to a site on a protein and causes a conformational change in the protein, but neither activates nor prevents activation of the protein. For our purposes, an allosteric regulator changes the conformation of a receptor, but does not activate a receptor. An allosteric regulator binds to a different place on the receptor than the neurotransmitter does; therefore, it doesn't prevent a neurotransmitter from binding to a receptor like a competitive antagonist does.

Allosteric regulators may augment or diminish a receptor's response to a neurotransmitter. We identify such substances as either *positive* or *negative modulators*. A **positive modulator** is a chemical substance that binds to an allosteric site on a receptor and increases the ability of a neurotransmitter to bind to and/or activate the receptor. A **negative modulator** decreases the ability of a neurotransmitter to bind to and/or activate a receptor.

**Positive modulator**
A chemical substance that binds to an allosteric site on a receptor and increases the ability of a neurotransmitter to bind to and/or activate the receptor

**Negative modulator**
A chemical substance that binds to an allosteric site on a receptor and decreases the ability of a neurotransmitter to bind to and/or activate the receptor

Many drugs act as positive or negative modulators for $GABA_A$ receptors. For example, a benzodiazepine drug such as alprazolam (*Xanax*) binds to an allosteric site, named the *benzodiazepine site*. When a benzodiazepine drug binds to this site, the receptor undergoes a change that enhances its affinity for binding to GABA. This ultimately leads to more activation of $GABA_A$ receptors. In this way, a benzodiazepine drug serves as a positive modulator for $GABA_A$ receptors. The drug sarmazenil also binds to benzodiazepine sites but serves as a negative modulator.[‡] Through

[‡]Sometimes the term *inverse agonist* is used instead.

causing a conformational change in the receptor, sarmazenil causes fewer $Cl^-$ ions to flow through the $GABA_A$ channel when it is activated by GABA (Yakushiji, Fukuda, Oyama, & Akaike, 1989).

## STOP & CHECK

1. A drug that prevents the activation of a receptor but does not bind to the same site as a neurotransmitter is called a _____.
2. A drug that increases the ability of an ionotropic receptor to be activated by a neurotransmitter is called a _____.

1. noncompetitive antagonist 2. positive modulator

## Adaptations to Chronic Drug Use

*Chronic* drug use is the repeated, usually daily, use of a drug. The body may react differently to a drug when administered chronically compared to an acute administration. Three types of changes from chronic drug use are sensitization, tolerance, and dependence (**Table 4.3**).

**Sensitization**
An adaptation that increases a drug's effects

Chronic drug administration may cause **sensitization**, an adaptation that increases a drug's effects. Nicotine's psychostimulant effects, for example, are generally exhibited soon after regular use of nicotine begins. For example, in laboratory rats, nicotine initially causes inhibitory effects on activity in laboratory rats in an *open field*—basically a box sufficiency large for rats to roam freely about. Drawn cross-patterned lines on the floor or photobeams on the walls allow researchers to record the amount of general movement via the number of line crosses or beam breaks. After several days of administration, nicotine induces an increase in number of line crosses—an indication of excitatory effects on general locomotor activity (Rosecrans, Stimler, Hendry, & Meltzer, 1989).

**Tolerance**
An adaptation that weakens a drug's effects, requiring greater doses to achieve desired drug effects

**Tolerance** refers to an adaptation that weakens a drug's effects, requiring greater doses to achieve desired drug effects. Tolerance, like sensitization, most often occurs from chronic administration. Some drugs cause tolerance after acute administration. Acute administration of nicotine, for example, causes an immediate change to nicotinic receptors that results in a temporary tolerance to nicotine's effects (Ochoa, Li, & McNamee, 1990).

**Review!** A dose-effect curve depicts the magnitude of a drug effect by dose, normally starting with doses with little effect up to doses with the drug's maximum effect (Chapter 1).

Pharmacologists can assess the effects of sensitization and tolerance through using dose-effect curves. In **Figure 4.11**, the dose-effect curve labeled "before

**TABLE 4.3 Sensitization, Tolerance, and Withdrawal**

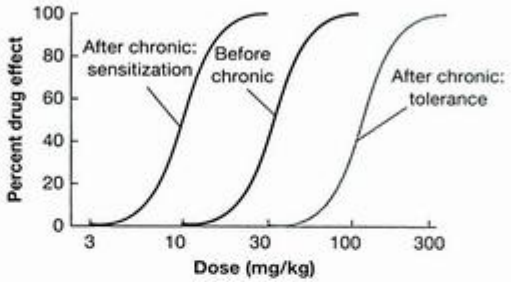
| Function | Type | Characteristics |
|---|---|---|
| Sensitization | | Increased responsiveness to a drug's effects |
| | Pharmacokinetic | Increases the amount of drug reaching its site of action |
| | Pharmacodynamic | Increased responsiveness at a drug's site of action |
| | Behavioral | Increased behavioral responsiveness |
| | Conditioned | Environmental stimuli elicit physiological effects that strengthen a drug's effect |
| | Cross tolerance | Sensitization to other drugs in the same class |
| Tolerance | | Drug adaptations require escalating drug doses to achieve desired effects |
| | Pharmacokinetic | Reduces the amount of drug reaching its site of action |
| | Pharmacodynamic | Reduced responsiveness at a drug's site of action |
| | Behavioral | Decreased behavioral responsiveness |
| | Conditioned | Environmental stimuli elicit physiological effects that weaken a drug's effect |
| | Cross tolerance | Tolerance to other drugs in the same class |
| Withdrawal | Physical | Physiological withdrawal symptoms such as nausea |
| | Psychological | Psychological withdrawal symptoms such as drug cravings or mood changes |

chronic" shows a drug's dose-effect curve prior to chronic administration. For the "before chronic" curve, a 10.0 mg/kg dose shows little effect and a 100.0 mg/kg dose shows a maximum effect. The curve "after chronic: sensitization" demonstrates a dose-effect curve following chronic administration of a drug that led to an increase in the effectiveness of the drug doses. In this case, a maximum drug effect is reached by a 30.0 mg/kg dose, and the 10.0 mg/kg dose produces a moderate effect (whereas, before chronic, the dose produced only a minimal effect). Pharmacologists refer to this pattern of sensitization illustrated on the graph as *a leftward shift*. You'll catch a pharmacologist saying things like "the curve shifted to the left," for example.

If, instead, a reduced effectiveness from drug doses were to occur, we would see the curve on the right, labeled "after chronic: tolerance." In this example,

**FIGURE 4.11 Dose-Effect Curves for Sensitization and Tolerance**

Due to chronic administration, the effectiveness of doses may change. The figure shows three dose-effect curves. The middle curve represents the drug's effectiveness (expressed as a percentage of effect, *y*-axis) by dose (*x*-axis) before chronic administration of a drug. If sensitization occurred following chronic administration, we would find the curve shift to the left; that is, doses have become more effective, and a maximum effect can be achieved with a lower dose. If tolerance occurred, we would find the curve shift to the right; that is, drug doses have become less effective, and a maximum effect requires a higher dose.




the 100.0 mg/kg dose, shown as maximally effective in the *before chronic* condition, now produces only a moderate effect. A 300.0 mg/kg dose must be used to reach a maximum effect. The pattern shows a *rightward shift*—if eavesdropping on a pharmacologist, you might hear "the curve shifted to the right," along with some additional statements allowing you to clearly deduce if this was the intended effect or not.

Multiple forms of adaptations to chronic drug administration that lead to sensitization or tolerance may occur from drug treatment: pharmacokinetic, pharmacodynamic, and behavioral (**Table 4.3**). We encounter these most often for interpreting tolerance, and thus, tolerance is mostly referred to in the following paragraphs. In each case, however, tolerance leads to weakened drug effects, whereas sensitization leads to strengthened drug effects. In the first form, **pharmacokinetic tolerance (or drug dispositional tolerance)**, pharmacokinetic actions reduce the amount of drug reaching its site of action. Often, pharmacokinetic tolerance causes an increased rate of drug conversion to metabolites. For example, a pharmacokinetic tolerance to alcohol occurs when increased levels of an enzyme, *alcohol dehydrogenase*, causes increased conversion of alcohol to its metabolite. By increasing the conversion of alcohol, alcohol dehydrogenase causes fewer alcohol molecules to reach the brain.

**Pharmacokinetic tolerance (or drug dispositional tolerance)**
Pharmacokinetic actions that reduce the amount of drug reaching its site of action

**Pharmacodynamic tolerance**
Reduced responsiveness to a drug at the drug's site of action

The second form of tolerance, **pharmacodynamic tolerance**, consists of a reduced responsiveness to a drug at the drug's site of action. Often, this occurs as

a change in the number of receptors available for drug binding at the site of action. The term *upregulation* refers to an increased number of receptors, whereas *downregulation* refers to a decreased number of receptors. Chronic administration of the anti-anxiety drug buspirone causes lower levels of serotonin receptors (Taylor & Hyslop, 1991). For buspirone, fewer serotonin receptors lead to weaker drug effects.

In the third form of tolerance, **behavioral tolerance**, a decreased behavioral responsiveness to a drug's effects occurs. Alcohol use provides a good example here as well. Studies show that moderate drinkers perform certain behavioral tasks under the effects of alcohol better than those who seldom drink alcohol do while under the effects of alcohol (Goodwin, Powell, & Stern, 1971; Sdao-Jarvie & Vogel-Sprott, 1991).

**Behavioral tolerance**
Decreased behavioral responsiveness to a drug's effects

Another form of tolerance is conditioned tolerance. **Conditioned** (or **contingent**) **tolerance** occurs as a physiological response to stimuli associated with substance use that serves to counteract a drug's physiological actions. We find this also referred to as *Pavlovian tolerance*. The physiological response might inhibit a drug's pharmacokinetic or pharmacodynamic actions, but this response will either not occur or be weaker when certain drug-associated stimuli are absent. When absent, the dependent organism will experience significantly greater effects, potentially including drug overdose.

**Conditioned (or contingent) tolerance**
Stimuli associated with substance use elicit compensatory actions that reduce a drug's effects

Tolerance to a drug's effects may carry over to drugs with similar biological actions. This form of tolerance is called **cross tolerance**. For example, those addicted to heroin can tolerate a much higher dose of the opioid replacement drug methadone than those not addicted to heroin.

**Cross tolerance**
Tolerance for other drugs with similar biological actions

Following chronic administration and the development of either sensitization or tolerance, ceasing use of the drug can lead to withdrawal symptoms. The term **withdrawal syndrome** refers to the collection of withdrawal symptoms for a drug. We classify withdrawal symptoms as either physical or psychological. For example, abrupt withdrawal of an antidepressant drug may lead to *physical withdrawal* effects, such as dizziness, nausea, or sensations of buzzing or electric shocks. For an addictive substance, *psychological withdrawal* effects commonly include drug cravings or mood changes. The presence of withdrawal symptoms has traditionally led to identifying users as "drug dependent," but current criteria for diagnosing addiction no longer include the term dependence, referring instead to withdrawal effects (American Psychiatric Association, 2013a).

**Withdrawal syndrome**
The collection of withdrawal symptoms for a drug

Withdrawal symptoms often result from the body's compensatory adaptive changes to drug actions. When a sufficient period of time without a drug administration occurs, the body's compensatory effects become evident and manifest themselves as withdrawal symptoms. For example, heroin initially produces euphoria, constipation, and pain relief, but after some period of chronic usage, the body develops a tolerance to these effects. Once a tolerance to heroin occurs, cessation of heroin use produces withdrawal symptoms that include depression, diarrhea, and exaggerated sensitivity to pain. Thus, the compensatory actions become withdrawal symptoms.

## STOP & CHECK

1. A defining feature of drug dependence is the presence of _____.
2. Adaptation to chronic drug administration, as indicated by a dose of drug no longer producing the same magnitude of effects, is called _____.

1. withdrawal symptoms 2. tolerance

## From Actions to Effects: Environmental Neurotoxicology

**Neurotoxins**
Substances that damage or destroy parts of the nervous system

*Environmental neurotoxicology* is a field devoted to the study of neurotoxins in the environment. **Neurotoxins** are substances that damage or destroy parts of the nervous system. The term *environmental*, in this context, is used in a broad sense, including your home, car, classroom, workplace, the outdoors, and anywhere else you encounter. In Flint, Michigan, residents were exposed to environmental toxins in their drinking water, for example, and young children in Flint were found to have significantly higher blood levels of lead following the water source change (Hanna-Attisha, LaChance, Sadler, & Champney Schnepp, 2016). Lead exposure among children correlates strongly to deficits in learning and motor coordination (de la Burdé & Choate, 1975; Koller, Brown, Spurgeon, & Levy, 2004). We can also encounter lead from paints used on pre-1980s buildings, especially chips or dust from walls—a particular problem during renovation projects.

Numerous types of neurotoxins exist. Lead serves as an example of heavy metals that we can easily encounter. Another common type of environmental neurotoxins consists of *endocrine disruptors*—named for their interference with the endocrine system, including dysfunctions in the reproductive system, nervous system, and immune system. We find endocrine disruptors in pesticides, plastics, flame retardants, and many types of building materials. In particular, many household plastics contain the endocrine disruptor bisphenol-A (BPA), one of the better-known endocrine disruptors. Another neurotoxin we may easily be exposed to is polychlorinated biphenyls (PCBs), compounds once found in electronic transformers and coolants. PCBs, which are highly fat soluble, serve as common environmental contaminants, and consumption of fish from waters containing PCBs represents a common source of PCB exposure in humans (Jensen, 1987).

Researchers study neurotoxins in the same ways that pharmacologists study psychoactive drugs. Neurotoxins may cause *neuronopathy* (the destruction of neurons), *myelinopathy* (the destruction of myelin sheathing), *axonopathy* (the destruction of axons), and *transmission toxicities* (damage to processes for neurotransmission). To continue using lead as an example, we find sweeping neurotoxic effects, including induction of excitotoxicity (cell damage or death due to excessive stimulation), diminished pools of synaptic vesicles for storing neurotransmitters, impaired myelination by oligodendrocytes, among many other direct and indirect effects (Lidsky &

Schneider, 2003). Findings such as these remind us of the importance of minimizing risk of exposure to industrial compounds, given the long-lasting effects these compounds can produce.

## STOP & CHECK

1. How might a neurotoxin disrupt neurotransmission?

1. A neurotoxin can affect neurotransmission in a variety of ways, including reversibly binding to enzymes or destroying synaptic vesicles.

## CHAPTER SUMMARY

The field of pharmacology is largely divided into two general areas: pharmacokinetics and pharmacodynamics. Pharmacokinetics concerns the passage of the drug through the body in four phases: absorption, distribution, biotransformation, and elimination. Absorption is the ability of a drug to enter the bloodstream, and this depends on the administration route used. Distribution refers to drug passage through the bloodstream to target sites. Drugs must possess certain properties to passively diffuse through the blood–brain barrier. Biotransformation refers to the process of enzymatically converting a drug into metabolites. Elimination is the process of expelling drugs from the body.

Pharmacodynamics are the mechanisms of action for a drug. The pharmacodynamics of a psychoactive drug consist of altering neurotransmission, including changes in neurotransmitter synthesis, storage, release, receptor binding, and conversion to metabolites. Drugs have the ability to activate receptors or to prevent the activation of receptors. Further, drugs can alter how well a neurotransmitter binds to and activates a receptor.

Chronic drug use can lead to dependence, tolerance, or sensitization. Drug dependence is shown when abstention from a drug causes withdrawal effects. Dependence occurs as either physiological dependence or psychological dependence. Users exhibit tolerance when they require higher doses to achieve similar effects. Tolerance occurs as pharmacokinetic tolerance, pharmacodynamic tolerance, or behavioral tolerance. Sensitization consists of an increase in responsiveness to a drug over time.

## KEY TERMS

Absorption 98
Liberation 101
Distribution 103
Bioavailability 103
Blood–brain barrier 103
Passive diffusion through the blood–brain barrier 103
Active transport through the blood–brain barrier 103
Nonspecific binding 104
Biotransformation (or metabolism) 105
Metabolite 105
Phase I biotransformation 105
Phase II biotransformation 105
Personalized medicine 106
First-pass metabolism (or first-pass effect) 106
Active metabolite 107
Prodrug 107
Elimination 107
Elimination rate 107
Half-life 107
First-order kinetics 107
Zero-order kinetics 108
Steady state (for drug concentrations) 108
Binding affinity 113
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Agonist 118
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CHAPTER 5

# Drugs of Abuse

## Chapter Outline

- Regulatory Agencies and Drug Classification
- Clinical Definitions and the Diagnosis of Drug Addiction
- Theoretical Models and the Features of Drug Addiction
- Drugs of Abuse and Reward Circuitry
- Chronic Use of Abused Substances and Changes to Learning and Memory Systems
- Neurobiology and the Stages of Drug Addiction
- Mortality and Drug Addiction
- Psychological and Pharmacological Therapies for Treating Drug Addiction
- From Actions to Effects: Food Addiction
- A Final Note About Drug Addiction

## Learning Objectives

- Assess the approaches for regulating substances of abuse
- Explain the purposes and limitations of clinical definitions for substance addiction
- Interpret scientific models for substance addiction
- Connect structures and systems in the nervous system to patterns of substance use in addiction
- Assess the primary approaches for treating substance use disorders

As first presented in Chapter 1, psychoactive drugs broadly fall into two categories: those intended for instrumental use and those intended for recreational use. If you recall, the major distinction between such drugs is a person's intent or motivation for using the substance. This chapter expands on the use of recreational drugs to consider problem drug use leading to abuse and addiction.

**Harrison Narcotics Act**
U.S. federal law passed in 1915 that restricted the sale of narcotics

**Controlled Substances Act**
U.S. federal law passed in 1970 that regulates sale and possession of drugs identified as controlled substances

**Controlled substances schedules**
A scheduling system mandated by the Controlled Substances Act that classifies a drug according to its drug abuse potential and medical use potential

## Regulatory Agencies and Drug Classification

In addition to describing drugs based on their intended use, we also characterize drugs by their legal status. Laws at the state and national levels limit the availability of drugs deemed to have a significant risk of abuse. One of the first national regulations on drugs of abuse was the **Harrison Narcotics Act** passed in 1915, which restricted the sale of narcotics, primarily opioid drugs, to only medical uses. Law enforcement officials interpreted these medical uses to exclude treating withdrawal symptoms in opioid addiction.

In 1970, the **Controlled Substances Act** first described drugs of abuse as *controlled substances*. The act required the legal regulation of certain drugs with abuse potential, and it led to a classification system of **controlled substances schedules** for ranking drugs by abuse potential and proven medical uses. This act led to a classification system that still exists today. **Table 5.1** shows a list of selected drugs of abuse, and their schedules, regulated in the United States.

The U.S. Drug Enforcement Administration (DEA) uses five schedules to categorize drugs of abuse. Lower schedule numbers indicate greater abuse potential than higher schedule numbers, based on the DEA's assessment of these drugs. All drugs scheduled II through V have established medical uses. For example, the

**TABLE 5.1 Selected Controlled Substances**

| Schedule | Controlled Substance |
|---|---|
| I | Heroin |
| | LSD |
| | Marijuana (cannabis) |
| II | Cocaine |
| | Morphine |
| | Phencyclidine (PCP) |
| III | Ketamine |
| IV | Alprazolam (*Xanax*) |
| V | Codeine |

*Source:* Adapted from the DEA Controlled Substances Schedules, www.deadiversion.usdoj.gov/schedules/index.html.

DEA assigned schedule V to codeine, an opioid drug considered to have less abuse potential than drugs in other categories. Codeine is a key ingredient in prescription strength cough syrups.

According to the DEA, schedule II controlled substances have high abuse potential, but also have legitimate medical uses. For example, the DEA assigns cocaine as schedule II because of its legitimate medical uses, such as acting as a local anesthetic. Schedule I controlled substances are classified as having high abuse potential and no legitimate medical uses. For example, the DEA scheduled the hallucinogenic drug lysergic acid diethylamide (LSD) as schedule I, based on the agency's view that LSD has high abuse potential and lacks medical usefulness. For similar reasons, the DEA also lists cannabis as a schedule I controlled substance.

Other countries use different scheduling systems for controlled substances. For example, the United Kingdom assesses the harm caused by abused drugs according to three classification levels. Class A drugs cause the most harm and carry the stiffest penalties for possession and drug dealing. These drugs include MDMA (Ecstasy), cocaine, and psychedelic mushrooms. Class C drugs cause the least harm and carry the lightest penalties for possession and drug dealing. This class includes barbiturates, ketamine, and gamma-hydroxybutyric acid (GHB). Class B drugs have a moderate potential for harm. Although marijuana regulations have relaxed in most countries, including many states in the United States, the United Kingdom elevated marijuana from class C to class B in 2009.

The United Kingdom presents different considerations for certain drugs than the United States. For example, the United Kingdom classified GHB as a class C compound, whereas the United States classified GHB as a schedule I controlled substance. Further, the United Kingdom classified marijuana as a class B compound, but the United States classified marijuana as a schedule I controlled substance.

Although the controlled substances schedules represent a standard labeling system for drug use risk, disagreements for drug schedules occur among practitioners and researchers. A well-known example of this is marijuana. According to the U.S. government, marijuana is a schedule I substance, indicating high abuse potential with no established medical uses. Yet, many states allow the use of marijuana for recreational and medical uses, placing state laws in conflict with federal law.

Critics also question the methods used for scheduling drugs. One area of concern regards a slow response to new drugs of abuse. In particular, many potentially dangerous so-called *club drugs* are not currently scheduled substances. The DEA schedules drugs only after accumulating sufficient scientific evidence and law enforcement drug use statistics. Thus, drug scheduling can take years. Adding to this, clandestine drug suppliers develop designer drugs, substances designed to circumvent existing drug schedules. Consider the designer drug 1,4-butanediol, also known as *one comma four*—this compound is a prodrug for GHB (Carai et al., 2002; Satta, Dimitrijevic, & Manev, 2003). The DEA lists GHB as a schedule I substance but doesn't list 1,4-butanediol.

**Review!** A prodrug is a physiologically weak or inactive compound metabolized in the body to produce an active drug (Chapter 4).

Nutt and colleagues (2007) offered an alternative approach for drug scheduling that provided a broader consideration of types of risks from substance use. They defined *harm* as consisting of physical harm, addiction, or societal harm. *Physical harm*, in their approach, included damage to the body, such as impairment of heart or liver function. *Addiction* consisted of an inability to stop taking a drug, along with other factors used in the clinical diagnosis of a substance use disorder. *Societal harm* ranged from harm to family and other social relationships to costs associated with health care and law enforcement. After developing these definitions, an expert panel rated 20 abused drugs according to harm subgroupings. **Table 5.2** shows ratings from this study for selected drugs.

The harm assessment by Nutt and colleagues reveals many differences with regulatory scheduling. Although the drugs heroin and cocaine rated highly for harm, the drugs GHB and MDMA (Ecstasy) rated low. In contrast, the United States classifies GHB and MDMA as schedule I substances, and the United Kingdom classifies MDMA as class A, but GHB as class C. Two noncontrolled substances, alcohol and tobacco, also made the list. The harm assessment study rated alcohol as the fourth most harmful substance and tobacco, which includes nicotine, as the ninth most harmful substance. Studies such as these have the potential to guide regulatory changes for controlling drugs of abuse. However, those learning about the science behind recreational and addictive drug use should keep in mind that drug scheduling simply classifies a drug's status for possession and use according to a legal system for government. Such schedules systems are not meant to serve as scholarly authorities on the actions or effects of psychoactive substances.

**TABLE 5.2 Harm Ratings for Selected Drugs of Abuse**

| Drug | Physical Harm | Addiction | Societal Harm |
|---|---|---|---|
| Heroin | 2.8 | 3.0 | 2.5 |
| Cocaine | 2.3 | 2.8 | 2.2 |
| Alcohol | 1.4 | 1.9 | 2.2 |
| Tobacco | 1.2 | 2.2 | 1.4 |
| Inhaled solvents | 1.3 | 1.0 | 1.5 |
| LSD | 1.1 | 1.2 | 1.3 |
| GHB | 0.9 | 1.2 | 1.3 |
| MDMA (Ecstasy) | 1.1 | 1.1 | 1.1 |

*Source:* Based on data from Nutt et al. (2007).

*Note:* Higher scores = most harmful.

## STOP & CHECK

1. How might the DEA schedule a drug with high abuse potential and no perceived medical uses?
2. How does the harm scheduling for MDMA offered by Nutt and colleagues (2007) differ from the DEA's controlled substances scheduling?

1. The DEA schedules drugs with these characteristics as schedule I. 2. Although the DEA considers MDMA a schedule I controlled substance, MDMA rated low for harm according to the study by Nutt and colleagues.

## Clinical Definitions and the Diagnosis of Drug Addiction

Although regulatory agencies classify substances based on abuse potential and potential medical uses, clinicians use precise criteria to define and diagnose drug addiction. Early clinical definitions of addiction focused on the development of tolerance, physical dependence, and craving. **Craving** consists of a strong urge to use a drug.

**Craving**
A strong urge to use a drug

These early clinical definitions describe an addiction to some drugs but not others. They clearly apply to heroin and alcohol, for example, which produce tolerance, manifest physical withdrawal symptoms, and elicit powerful cravings. Yet, these definitions may fail to classify a drug such as cocaine as an addictive substance because it causes few physical withdrawal symptoms.

**Review!** Tolerance is an adaptation to a drug that requires a user to take escalating doses to achieve desired drug effects (Chapter 4).

More recent clinical definitions of drug addiction are provided in the fifth edition of the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) (2013a) and the World Health Organization's *International Statistical Classification of Diseases and Related Health Problems* (ICD-11) (World Health Organization, 2018). The definitions listed in these diagnostic manuals are similar, so only the DSM criteria are described here.

The DSM refers to addiction as a *substance use disorder*, which is defined as "a cluster of cognitive, behavioral, and physiological symptoms indicating that the individual continues using the substance despite significant substance-related problems" (p. 483). These symptoms include tolerance; withdrawal; a persistent desire to reduce use of the substance (although use continues); significant time spent in drug seeking and taking; replacing important activities with substance use; and continued use despite knowledge of social, physical, or psychological problems.

The current DSM differs from earlier clinical definitions because it considers drug use that persists despite a strong desire to stop. Furthermore, the DSM recognizes that drug use may continue despite the user's knowledge of physical or psychological harm to oneself and the toll that drug use takes on valuable social relationships and occupational activities.

According to the DSM's definition, both cocaine and cannabis can produce substance use disorders. Cocaine has the ability to produce strong cravings, produce tolerance, and compete with valuable social and occupational activities and other important natural reinforcers. Those who develop a substance use disorder for cannabis most often report "persistent desire or unsuccessful efforts to reduce or cease use" along with other DSM symptoms, such as continued use despite health problems and craving cannabis during withdrawal (Coffey et al., 2002).

**Relapse**
Return to a chronic drug use state that meets the clinical features of a substance use disorder

Clinicians consider addiction to be a chronically relapsing disorder that may require years of treatment. **Relapse** consists of a return to chronic drug use and exhibiting features of the substance use disorder. Given the propensity for relapse, one diagnosed with a substance use disorder does not become cured from treatment; rather, an individual reaches a state of remission.

The DSM addresses remission by sorting out conditions surrounding remission into different categories. These remission categories consist of "'in early remission,' 'in sustained remission,' 'on maintenance therapy,' and 'in a controlled environment'" (p. 484). In general, *early remission* corresponds to an individual meeting none of the criteria for a substance use disorder for a period of a few months to less than a year. *Sustained remission* refers to meeting none of these criteria for a year or longer. *Maintenance therapy* indicates that the individual does not meet the criteria for a substance use disorder while the individual is participating in a treatment program. In particular, maintenance therapy can refer to medication intended to address drug craving or warding off withdrawal symptoms, such as an opioid medication like buprenorphine. Remission might also be occurring in a *controlled environment*, such as living in an environment where drugs are not available. The last two remission types caution that an individual might relapse without taking a particular medication or after leaving a treatment facility.

## Theoretical Models and the Features of Drug Addiction

**Models of drug addiction**
Scientific attempts to characterize and explain compulsive drug use

Theoretical **models of drug addiction** attempt to characterize and explain compulsive drug use. They derive from scientific research and serve as a basis for extensive scientific studies, including assessing patterns of human drug use or basic laboratory research, to understand the factors behind addictive behavior. The characteristics and theoretical reasons for addiction derived from addiction models may differ from those described by clinical definitions, such as the DSM-5. Though we can learn about drug addiction from the DSM-5, the primary purpose of the DSM-5 or any other diagnostic manual is to develop a correct diagnosis for the disorder. Correctly diagnosing a disorder means that a clinician can design a treatment plan for his or her patient. Many addiction models utilize behavioral concepts and principles to

explain compulsive drug use, while other models heavily consider changes that take place in neurological systems.

## Associative Learning Principles Used in Addiction Models

Many drug addiction models use associative learning principles to characterize drug use. **Associative learning** is the process by which an organism learns associations between stimuli or between behaviors and stimuli. Much of associative learning theory comes from operant conditioning and classical conditioning.

**Associative learning**
Process by which an organism learns associations between stimuli or between behaviors and stimuli

During operant conditioning, consequences modify the occurrence and form of behavior (Skinner, 1938). The term **reinforcement** refers to a process in which the resulting consequence from a response increases the frequency of future responses. Said another way, reinforcing outcomes strengthen behavioral tendencies. Of course, the effectiveness of a reinforcer (a stimulus used during the process of reinforcement, such as a food pellet) depends largely on the current level of motivation. Food pellets work far better as reinforcers for a hungry lab rat, versus a full lab rat, for example.

**Reinforcement**
Process in which the resulting consequence from a response increases the frequency of future responses

We also use the terms *negative* and *positive* when discussing reinforcers. In this usage, *negative* refers to the removal of a stimulus, and *positive* refers to the addition of a stimulus. An example of a positive reinforcement context is a hungry rat pressing a lever to earn food pellets. The food pellets serve as positive reinforcers. An example of a negative reinforcement context is a rat pressing a lever to remove some type of aversive stimulation, such as a bright light. Removal of the bright light serves as a negative reinforcer. When responding no longer leads to reinforcers, the rate of responding declines over time—a process referred to as *extinction*.

A **conditioned stimulus** may develop from presenting stimuli in the presence of a stimulus involved in an associative learning process. Using one of the previous examples, a tone might acquire reinforcing properties if the tone repeatedly occurs in the presence of food. If a hungry rat then emits responses in order to activate only the tone, we refer to the tone as a *conditioned reinforcer*.

**Conditioned stimulus**
A stimulus that acquires the behavioral controlling properties of another stimulus that is involved in an associated learning process

Associative learning may occur during certain conditions or in environmental contexts. We describe one type of condition as a **discriminative stimulus**, which is a stimulus that, when present, signals the availability of reinforcement. Reinforcers are unavailable when the discriminative stimulus is absent. For the hungry rat just described, a discriminative stimulus might consist of a soft tone during experimental procedures. Lever presses result in food reinforcers when the tone is on but not when the tone is off.

**Discriminative stimulus**
A stimulus that, when present, signals the availability of reinforcement

Classical conditioning procedures describe how stimuli can elicit behavioral responses. The behaviors occur reflexively, whereas operant-conditioned behaviors occur as a result of past consequences. Described another way, classical conditioning consists of stimuli eliciting responses, whereas operant conditioning consists of responses producing stimulus outcomes.

Russian physiologist Ivan Pavlov (Pavlov & Anrep, 1927) first described behavior in terms of classical conditioning relationships. First, we recognize that many unlearned behaviors exist, such as Pavlov's description of food in the mouth eliciting salivation. We do not learn to salivate when food is in the mouth; it's simply a natural reflex. Second, Pavlov found that associations can develop, through conditioning,

between other stimuli and those that produce natural reflexes. This work led to the following terms to define stimulus–response relationships.

An *unconditioned stimulus* (UCS) consists of a stimulus that elicits a reflexive response, which is referred to as an *unconditioned response* (UCR). Food in the mouth serves as a UCS, and salivation serves as a UCR. A stimulus not part of this association, such as a light or tone, will not naturally elicit salivation; given this lack of association, we refer to such stimuli as *neutral stimuli*. By repeatedly pairing a neutral stimulus with a UCS, the neutral stimulus may incur associative properties that enable the stimulus alone to elicit salivation. When this occurs, the stimulus serves as a *conditioned stimulus* (CS); to describe salivation as elicited in this conditioned associative process, salivation is identified as a *conditioned response* (CR).

**Latent inhibition**
A resistant or slower conditioning process that occurs from using a familiar stimulus in an associative learning process

The ability to condition a stimulus is subject to the principle of latent inhibition. **Latent inhibition** consists of a resistant or slower conditioning process that occurs from using a familiar stimulus in an associative learning process. In this case, *familiar* suggests that the stimulus already belongs to at least one other associative learning process. Incorporating a familiar stimulus into a new associative learning process tends to be comparatively slower than incorporating an entirely novel stimulus into an associative learning process.

**Incentive salience**
Attribution of salient motivational value to otherwise neutral stimuli

Conditioning may also occur for motivational states. In particular, a motivational concept called **incentive salience** serves as an important part of modern drug addiction theory: It is the attribution of salient motivational value to otherwise neutral stimuli. These attributions can occur through associations of neutral stimuli with rewarding stimuli. When presented, incentivized stimuli command an individual's attention and elicit a motivation to pursue these and associated stimuli. The incentive-salience model for drug addiction, described later, utilizes this concept to explain compulsive drug use, where the presentation of stimuli incentivized through associations with drug use may motivate users to engage in drug seeking. The incentive-salience model also relates incentive-salience function to neural systems (Robinson & Berridge, 2003).

**Goal-directed behavior**
Behavior that occurs when an organism engages in learned behaviors in order to achieve a desired goal

We also have goal-directed behaviors, which may play an important role in decision making. **Goal-directed behavior** occurs when an organism engages in learned behaviors in order to achieve a desired goal. The topic of goal-directed behavior encompasses a large area of study approached from different areas of psychology, including cognitive and social psychology. Many frameworks for explaining and characterizing goal-directed behavior use associative learning principles, particularly in reference to drug-seeking behavior.

Many theorists use associative learning principles to characterize goal-directed behavior, particularly when describing this behavior during drug seeking. In this context, conditioned associations between responses and outcomes govern goal-directed behavior (de Wit & Dickinson, 2009). Neuroscientists tend to relate goal-directed behavior to the brain's reward system and the involvement of these pathways with the brain's learning and memory systems (Goto & Grace, 2005; Pennartz, Ito, Verschure, Battaglia, & Robbins, 2011).

Given all of the processes that govern behavior, behavioral pharmacologists have a keen interest in how drugs may affect these individual processes and, in that particular way, alter behavior. In this way, behavioral pharmacologists study the *behavioral mechanisms of drug actions*, a drug's effect on processes that govern behavior (Pitts, 2014).

For example, let's say we have a hungry rat working away on a lever in order to earn an occasional food pellet. However, pellets only come out when a stimulus light is turned on. We'll give this situation some terms. Positive reinforcers refer to food pellets, and motivation refers to the rat's level of hunger. The stimulus light serves as a discriminative stimulus.

We administer the rat a drug, wait long enough for the drug to produce an effect, and then find that the effect consists of an increased rate of lever pressing. What behavioral processes could the drug have affected? To suggest answers for this question, we can think through the various ways that the behavior is governed. The drug might have increased the rat's degree of hunger. Thus, greater motivation to eat led to more responses to earn food pellets. The increased rate might have led the rat to respond more often when the stimulus light was off—in this case, maybe the drug altered the rat's ability to discriminate situations from when the light was on versus when the light was off. Maybe the drug diminishes vision? The drug might have increased speed of movement—an effect observed by psychostimulant drugs. Might the drug have enhanced sense of taste of the pellets? In this case, each pellet becomes more reinforcing, and thus, the rat might respond more quickly to earn more of them. The example presents a lot of hypotheticals, but it illustrates how a behavioral pharmacologist ponders and examines the effects of drugs on specific behavioral processes in order to fully understand how a drug alters behavior.

## Drive, Opponent-Process Theory, and Incentive-Salience Models of Drug Addiction

**Drive theory of drug addiction** Repeated drug use that causes a motivation, or drive, to engage in seeking a drug's positive reinforcing effects

In 1952, Abraham Wikler provided one of the first drug addiction models to consider drug effects as behavioral variables. Based on studies with individuals addicted to opioid drugs, Wikler stated that drug-addicted individuals developed a drive to achieve a drug's positive reinforcing effects (**Table 5.3**). We refer to this as the **drive theory of drug addiction**.

**TABLE 5.3 Addiction Models**

| Addiction Model | Characteristics |
|---|---|
| Drive theory | Individuals experience a powerful drive to seek out and achieve a drug's positive reinforcing effects. |
| Opponent-process theory | Drug use that initially occurred to seek the rewarding effects of drugs now occurs in order to avoid or remove withdrawal effects. |
| Incentive salience | Stimuli associated with drug use have salient incentive value, and therefore draw a user's attention and create a motivational state to use the addictive substance. |
| Disease | The characteristics of drug addiction correspond to the medical definition of a disease. |

This drive consists of a motivation to seek a drug's effects. In this model, drive attains strong, irresistible levels that compel drug seeking and use, with the level receding after use. Moreover, the withdrawal effects occurring as time goes by since the last drug use serve to re-strengthen an individual's drive to obtain and use the drug. In this regard, drive theory considers drugs to be positive reinforcers, and the degree of strength of the reinforcer corresponds to the degree of drive experienced by the user.

**Opponent-process theory of drug addiction**
The effects of a drug that are automatically counteracted by opposing actions in the body

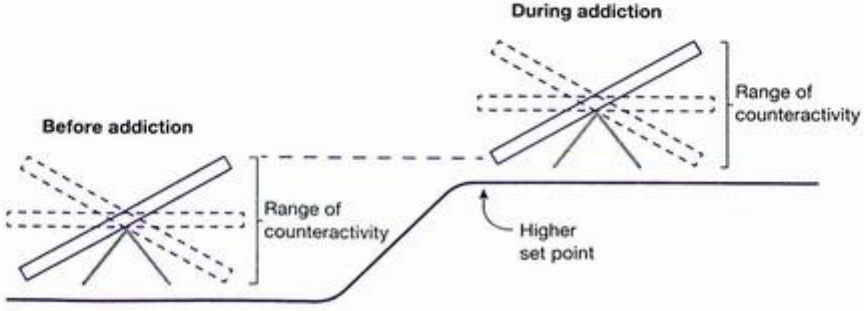
Solomon and Corbit (1974) offered the opponent-process theory as another explanation for drug use during addiction (Table 5.3). According to the **opponent-process theory of drug addiction**, the effects of a drug are automatically counteracted by opposing actions in the body. During addiction, the brain may, for example, elicit anhedonic effects to counteract a drug's hedonic (i.e., pleasurable) effects. These opposing actions may attempt to bring the body back to a physiological equilibrium in order to maintain normal processes at a particular setpoint.

**Allostasis**
The maintenance of a physiological state around a setpoint that has deviated from the body's normal setpoint

While this can be conceptually viewed as homeostasis, the constant demands on physiological systems in order to offset the chronic effects of addictive substances may lead to a shifting of the homeostatic setpoint beyond the body's typical range. Instead, addiction researchers refer to this counteraction process as **allostasis**, the maintenance of a physiological state around a setpoint that has deviated from the body's normal setpoint (Koob & Le Moal, 2001). In this way, physiological systems, including brain systems involved in addiction, become balanced around a new normal. This concept applies well to drug-addicted individuals who no longer gain adequate satisfaction from natural rewards—the setpoint has adjusted upward as the brain adapts to the far greater rewarding effects achieved by abused drugs (**Figure 5.1**).

**FIGURE 5.1 Allostasis Concept in Addiction**

The body works to maintain physiological activity around a particular setpoint, as illustrated in the teeter-totters in this figure. A perfectly balanced teeter-totter is ideal, and the range of activity is limited by the parameters of the system (shown as the ground in this picture). This concept continues during addiction, except that the setpoint changes, as shown by the teeter-totter on the right, set up on a hill. Even the "ground level" during addiction is above the highest level for the "before addiction" teeter-totter on the left. If these teeter-totters represented a drug high, the highs achieved by natural rewards before addiction are incapable of reaching the levels experienced and expected during addiction.



As illustrated in **Figure 5.2**, the sum of a drug's effects and its opposing processes defines an individual's subjective experience. If a drug's effects outweigh those from opposing processes, then an individual will experience the drug's effects. However, if effects generated from opposing processes significantly outweigh drug effects, then an individual will experience withdrawal effects. A balanced state occurs when drug effects equally balance against opponent-process effects.

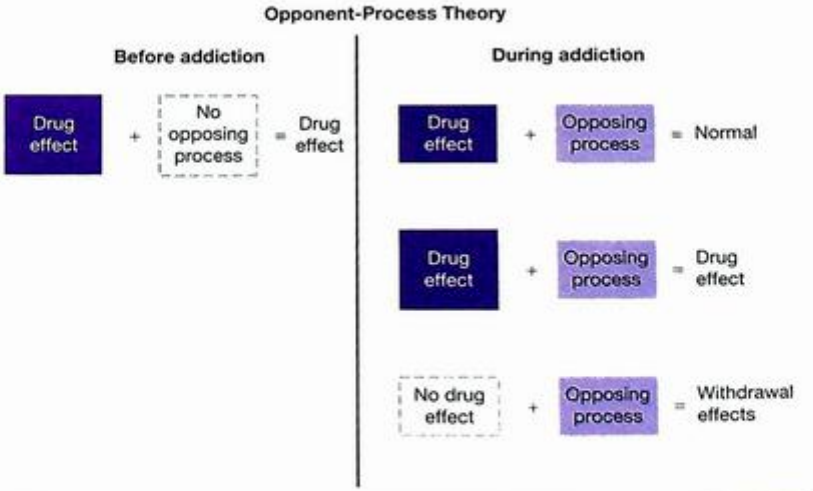
The type of reinforcement governing addictive behavior also distinguishes between Wikler's drive model and Solomon and Corbit's opponent-process theory. Unlike drive theory, the opponent-process theory considers that addictive drug use occurs partly to remove or prevent withdrawal symptoms. Thus, during the development of addiction, motivations for drug use can shift from achieving reinforcing effects, in a positive reinforcement context, to ridding or avoiding withdrawal symptoms, in a negative reinforcement context.

**Incentive-salience model** Drug addiction that occurs after a shift from "liking" the effects of a drug to "wanting" the effects.

The **incentive-salience model** states that drug addiction occurs after a shift from *liking* the effects of a drug to *wanting* the effects of a drug. *Wanting* occurs in an incentive-salience context, whereby stimuli associated with drug use command attention and elicit a salient motivational state toward pursuing the drug (Robinson

**FIGURE 5.2 Opponent-Process Theory**

According to the opponent-process theory of drug addiction, opposing processes counter the effects of an abused drug. Before addiction occurs (left panel), few, if any, processes counteract a drug's effects. During addiction, opponent processes counteract a drug's effects. Equally balancing drug effects and opposing processes lead to a balanced state (top, right panel), whereas overpowering drug effects can overcome opponent processes (middle, right panel). Withdrawal effects occur when opposing processes occur in the absence of drug effects (bottom, right panel). See text for further information.



& Berridge, 2003). In a technical sense, *wanting* in this model represents the process of developing and expressing incentive salience, whereas the term *craving*, in a basic sense, simply refers to a desire to use a drug (Sayette et al., 2000). *Liking* refers to the enjoyment of a drug's effects, which, according to this model, fails to entirely explain drug addiction. In fact, the incentive-salience model may explain why addicted users may *want* a drug more while, as tolerance develops, *liking* the drug less (Robinson & Berridge, 2003).

Incentive salience may also offer an explanation for relapse in drug addiction. Through conditioning, such incentivized stimuli may serve as reminders of former drug use; when encountered, they may implicitly engage motivational states for drug use. As described in **Box 5.1**, researchers study conditions that reinstate drug self-administration responses in animals in an effort to better understand why relapse occurs.

# BOX 5.1

## SELF-ADMINISTRATION

*Self-administration procedures* use drugs as reinforcers for operant responding in animals. In a typical self-administration procedure, an animal learns to respond to an operandum such as a lever to receive an injection of the drug. The drug is usually delivered intravenously through a surgically implanted intravenous catheter. When drugs serve as positive reinforcing stimuli, drug injections alone are entirely capable of initiating self-administration responses. For example, if a cocaine injection occurred whenever a rat pressed a lever, then cocaine's reinforcing effects would occasion further lever pressing.

The self-administration procedure provides an important analogue for human drug use. As reviewed in this chapter, chronic use of an abused drug incorporates brain systems important for learning. In the self-administration procedures, animals also learn to take drugs of abuse. Beyond this, self-administration procedures provide measurements of a drug's reinforcing strength. In doing so, self-administration procedures provide an indication of a drug's potential for causing addiction.

We measure a drug's reinforcing strength by determining its *break point*, the maximum amount of response effort an organism will devote toward receiving an administration of a drug. Break point studies normally employ *progressive-ratio reinforcement schedules*, which gradually increase the number of responses necessary to achieve a drug administration.

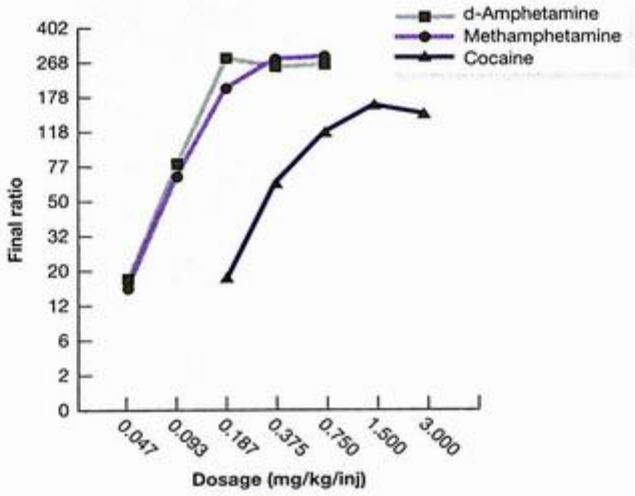
**Box 5.1 Figure 1** shows data from rats that self-administered any of several psychostimulant drugs on a progressive-ratio schedule (Richardson & Roberts, 1996). For d-amphetamine and methamphetamine, rats pressed the lever as many as 268 times to receive an injection. For cocaine, rats pressed the lever as many as 178 times to receive a drug injection. These maximum numbers of lever presses define each drug's break point at a given dose.

Researchers also employ other drugs to modify self-administration. For example, Maric and colleagues (2012) administered the hunger-stimulating hormone ghrelin to rats trained to self-administer heroin (**Box 5.1 Figure 2**). In this study, ghrelin administration increased the break point for heroin, suggesting that ghrelin enhanced heroin's reinforcing effects.

Researchers also use self-administration procedures to assess *reinstatement*, the recurrence of drug self-administration responding after a period of extinction. Reinstatement may provide an analogue of drug relapse

## BOX 5.1 FIGURE 1 Break Points in a Self-Administration Study

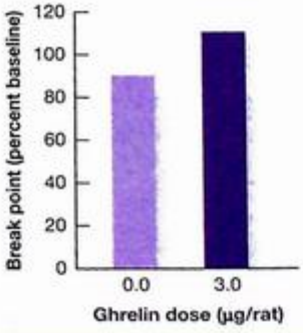
Break points consist of the maximum number of lever presses an animal will emit for a drug injection. The *y*-axis shows the final reinforcement ratio, defined as the total number of lever presses needed to earn a reinforcer, and the *x*-axis shows the dosage of drug administered per injection.




*Source:* Adapted from Richardson and Roberts (1996).

## BOX 5.1 FIGURE 2 Effect of Ghrelin on Self-Administration for Heroin

The hunger-stimulating hormone ghrelin increased the break point for self-administered heroin. The *y*-axis shows the break point value compared to baseline responding, and the *x*-axis shows the amount of ghrelin provided to the rats.




*Source:* Adapted from Maric, T., Sedki, F., Ronfard, B., Chafetz, D., & Shalev, U. (2012). A limited role for ghrelin in heroin self-administration and food deprivation-induced reinstatement of heroin seeking in rats. *Addiction Biology*, 17: 613–622. doi:10.1111/j.1369-1600.2011.00396.x.

*(Continued)*

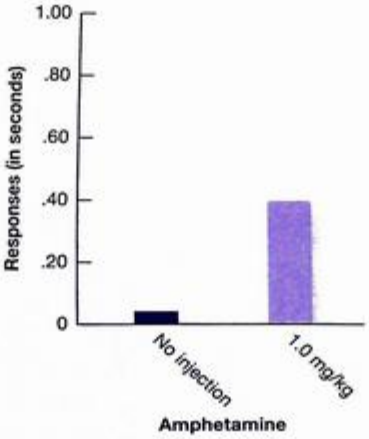
(Continued)

in humans. The general procedure for reinstatement goes as follows. After animals learn to self-administer a drug, researchers disable the operandum, resulting in an extinction period when responding no longer achieves a drug infusion. Over time, responding reduces substantially. At this point, a researcher may cause responding to occur by giving the animal an injection of drug (drug-induced reinstatement), eliciting a stimulus previously paired with drug delivery (cue-induced reinstatement), or delivering a brief shock or other aversive stimulus (stress-induced reinstatement).

In one of the first demonstrations of drug-induced reinstatement, Gerber and Stretch (1975) extinguished self-administration responding for cocaine by replacing cocaine with saline in the chamber's infusion syringe. After responding decreased to a low level, these researchers gave the monkeys an infusion of the psychostimulant drug d-amphetamine, which resulted in a return to self-administration responding, despite still having saline in the syringe. **Box 5.1 Figure 3** provides the findings from this experiment.

## BOX 5.1 FIGURE 3 Drug-Induced Reinstatement of Self-Administration

A pre-session infusion of d-amphetamine caused monkeys trained to self-administer cocaine to resume self-administration responding. For the data shown, the infusion syringe contained only saline. The left bar shows self-administration responding, and the right bar shows self-administration responding after an injection of d-amphetamine (1.0 mg/kg).




*Source:* Data from Gerber and Stretch (1975).

## STOP & CHECK

1. Compare the clinical definitions for addiction for cocaine.
2. How does the opponent-process theory of drug addiction account for drug withdrawal?
3. According to the incentive-salience model, what are the characteristics of drug wanting?

1. Early definitions for addiction may fail to consider cocaine as addictive because it has few physical withdrawal symptoms. However, the modern DSM definition for addiction incorporates other features of cocaine use, including an inability to quit despite wanting to. 2. During drug addiction, the body automatically elicits opposing processes to regain homeostasis and normal brain functioning. When a drug is absent, effects resulting from these unchecked opposing processes occur as withdrawal effects. 3. Drug wanting consists of a motivational state elicited by stimuli incentivized through associations with drug use.

### Disease Model of Drug Addiction

**Disease model**
Model that characterizes drug addiction as a disease

The **disease model** characterizes drug addiction as a medical disease (Table 5.3). To put this in perspective, consider the definition for a disease offered by *Stedman's Medical Dictionary* (Stedman, 1999): "An interruption, cessation, or disorder of body function, system, or organ." When considering drug addiction as a disease, one may thus determine how drugs of abuse may interrupt, cease, or disrupt functions in the body. Diseases also have causes, such as a pathogen, and the degree of susceptibility to disease may depend on one's potential to have a predisposition for the disease.

Those who advocate this model affirm that the substance serves as the cause of the disease. Thus, just as a disease may disrupt physiological processes, drugs also can disrupt neurological processes causing addictive behaviors. From this viewpoint, we can think of relapse as the re-emergence of the neurological processes underlying addiction that cause a return to regular substance use.

Further, one may possess a predisposition for drug addiction, just as one may have a predisposition for other diseases. In addition to drawing connections between a disease's characteristics and addictive behavior, advocates of this model argue that defining addiction as a disease allows medical treatment of the disease. The goal of treatment, then, is to manage the disease. The disease model is also a central perspective for abstinence-based 12-step recovery programs such as Alcoholics Anonymous and Narcotics Anonymous, which are discussed later in this chapter.

## Drugs of Abuse and Reward Circuitry

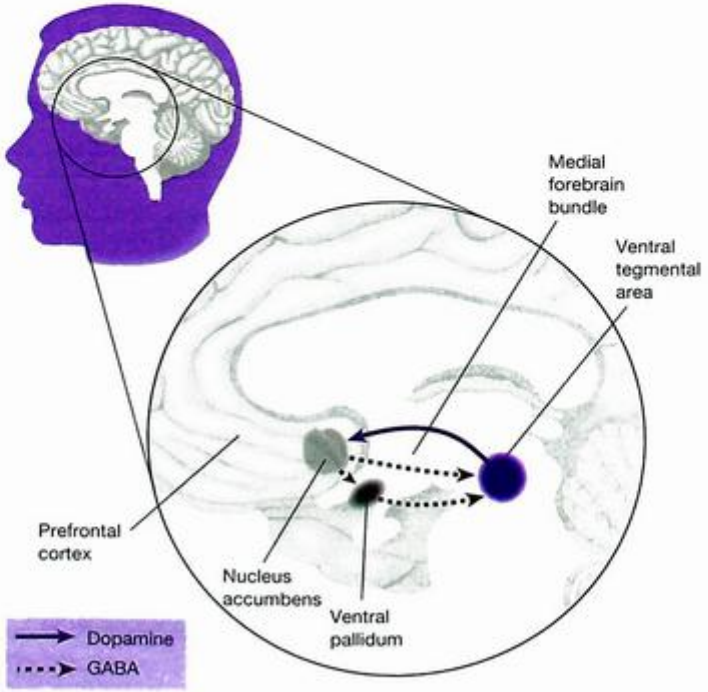
Drugs of abuse act directly or indirectly on the brain's reward circuitry (**Figure 5.3**). A key portion of this circuitry consists of mesolimbic dopamine neurons that originate in the ventral tegmental area and terminate in the nucleus accumbens. Dopamine release in the nucleus accumbens produces rewarding effects, and this particular

action accounts for the rewarding effects of many drugs of abuse, such as cocaine and amphetamine, which we cover in the next chapter. In addition, we find neurons for GABA exiting the nucleus accumbens and terminating back to the ventral tegmental area, in addition to another structure called the ventral pallidum. GABA neurons from the ventral pallidum also terminate in the ventral tegmental area.

The effect dopamine has on GABA neurons in the nucleus accumbens depends on the dopamine receptors activated. We find excitatory $D_1$ receptors on GABA neurons that originate in the nucleus accumbens and terminate in the ventral tegmental area. On the other hand, we find inhibitory $D_2$ receptors on GABA neurons that originate

**FIGURE 5.3 Brain Reward Circuitry**

The *reward system* is made up of mesolimbic dopamine neurons that originate from the ventral tegmental area and terminate in the nucleus accumbens. The release of dopamine in the nucleus accumbens inhibits GABA neurons and produces rewarding effects. GABA neurons in the ventral tegmental area inhibit the activity of dopamine neurons by activating inhibitory GABA receptors. Thus, some GABA neurons directly form a negative feedback loop from the nucleus accumbens to the ventral tegmental area. Other GABA neurons lead from the nucleus accumbens to the ventral pallidum, and the ventral pallidum also sends GABA neurons to the ventral tegmental area.



in the nucleus accumbens and run instead to the ventral pallidum (Cooper, Robison, & Mazei-Robison, 2017; Wise, 2002). These and many other structures make up or influence reward circuitry, and we'll bring more into the picture as we go about learning the actions of different types of psychoactive drugs throughout the book.

**Review!** The axons in the mesolimbic dopamine pathway terminate in the nucleus accumbens as well as other limbic system structures, including the amygdala and hippocampus (Chapter 3).

We attribute the discovery of the brain reward system to James Olds. In collaboration with Peter Milner, a graduate student also working in the lab, Olds published his discovery in 1954 (Olds & Milner, 1954). The report they published provided an assessment of electrodes placed in different parts of the forebrain.

To demonstrate these reinforcing effects, Olds and Milner designed an operant chamber equipped with a lever; when pressed, the lever activated the brain electrode. In this way, the researchers provided an apparatus by which rats governed the number of times they received electrical stimulation (**Figure 5.4**).

Since this original study, Olds and many other researchers further investigated this newly discovered system of reward in the brain in a host of different organisms, including humans. Olds wrote a paper reviewing the constellation of findings about this system some years later (Olds, 1962). Taking a look at all of these findings, Olds noted that greater reinforcing effects occurred from electrodes placed in the *medial forebrain bundle*, an area expanding between the nucleus accumbens and the ventral tegmental area. We now know that mesolimbic dopamine axons traveling to the nucleus accumbens pass through the medial forebrain bundle. In general, we account for the reinforcing effects produced by stimulation of the medial forebrain bundle as due to increased dopamine release in the nucleus accumbens (Nakahara, Ozaki, Miura, Miura, & Nagatsu, 1989).

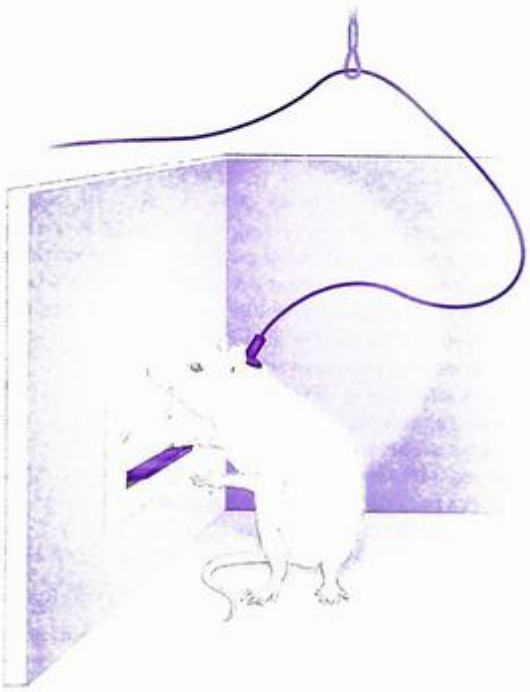
The discovery by Olds and Milner revealed a system or circuit for producing rewarding effects, but the researchers lacked sufficient information to understand the physiological nature of this circuit. In fact, the notion that chemical molecules, rather than electricity, were the basis for communication between neurons had only recently been settled. In biological psychology textbooks (e.g., Garrett, 2015), we learn about Otto Loewi's 1921 experiment to demonstrate chemical transmission from neurons. Otto Loewi took two frogs, exposed the chest cavity in each, and in only one of the frogs electrically stimulated the vagus nerve that runs to the heart. Vagus nerve stimulation decreased the frog's heart rate; when the heart rate decreased, Loewi collected fluid around the heart and applied the fluid around the other frog's heart. The other frog's heart rate also decreased—thus, he concluded that chemical molecules, rather than simply ions in an electrical sense, must be the mode of communication between neurons.[1]

Yet, we don't typically learn from biological psychology textbooks that Loewi failed to replicate his experiment and that others did as well. His methods were criticized

[1]We now know that some synapses are, in fact, electrical, but most are chemical.

**FIGURE 5.4 Intracranial Self-Administration**

In the seminal experiment by Olds and Milner, a rat learned to press a lever at a high rate to achieve the reinforcing effects produced by the electrodes. Electrodes placed in and around the medial forebrain area led to the highest rates of responding, likely activating mesolimbic dopamine neurons that terminate in the nucleus accumbens.



and the discovery written off as an anomaly. Eventually, the chemical acetylcholine was identified within the substance he had collected, and acetylcholine was known at the time to rapidly degrade in the presence of the enzyme acetylcholinesterase.

This finding led to a hypothesis concerning the irreproducibility of Loewi's frog experiment—perhaps acetylcholine degraded too rapidly for it have an effect after it was collected and transferred. In 1926, Loewi added an acetylcholinesterase inhibitor to his experiment to prevent the breakdown of acetylcholine. This time, transfer of the substance from around the heart of the first frog, which received stimulation of the vagus nerve, now inhibited the heart rate of the second frog, which did not receive the stimulation (Loewi & Navratil, 1926; Rubin, 2007). The finding was repeatable and is now regarded as the critical study proving that chemical neurotransmitters,

not electrical conductance, were the primary messengers of neuronal communication. However, studies purporting electrical conductance as this mode of communication still persisted into the late 1940s (e.g., Eccles, 1948), but the issue was finally settled in the mid-1950s (e.g., Eccles, Fatt, & Koketsu, 1954; Rubin, 2007).

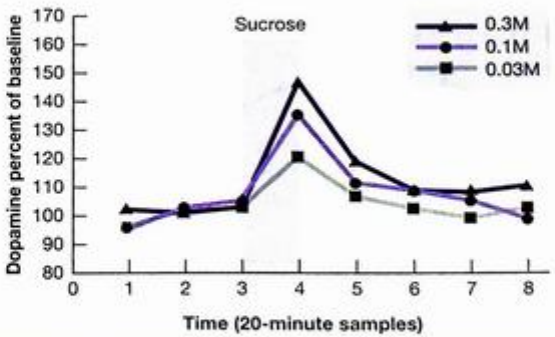
Thus, the discovery by Olds and Milner in 1954 came at a time when the study of modern theories on neurotransmission were in their infancy. A few years after Olds reported on a reward system for the brain, Kathleen Montagu discovered the existence of dopamine in the brain (Montagu, 1957). In 1958, Arvid Carlsson first reported that dopamine likely had some functional significance for brain function as it was affected by treatment with the drug reserpine (Carlsson, Lindqvist, Magnusson, & Waldeck, 1958). Perhaps dopamine was another chemical messenger. Numerous studies conducted during the 1960s and early 1970s utilized new research techniques to investigate dopamine, revealing the major pathways for dopamine in the brain.

Today, as noted earlier, we know that reinforcing effects occur from increased dopamine release in the nucleus accumbens. Under natural conditions, nucleus accumbens dopamine levels elevate in the presence of stimuli that predict positive outcomes. Such stimuli include those to meet basic physiological needs, such as food and water, along with complex social or cultural reinforcers. Thus, behavioral neuroscientists consider dopamine as a critical neurotransmitter for goal-directed behavior.

For example, Hajnal, Smith, and Norgren (2004) used a microdialysis procedure to assess nucleus accumbens dopamine level changes elicited by food. At times during the procedure, rats consumed a sweet-tasting sucrose liquid food mix. When the sucrose mix was consumed, nucleus accumbens dopamine levels increased; dopamine levels returned to baseline levels after consumption of the food ceased (**Figure 5.5**).

**FIGURE 5.5 Sucrose Consumption and Dopamine Release**

Sucrose consumption elicited significant dopamine level increases in the nucleus accumbens in rats as revealed by microdialysis. M = molality, an index of concentration.



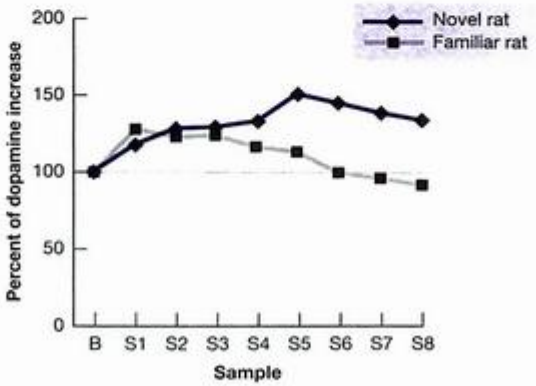

*Source:* Adapted from Hajnal, Smith, and Norgren (2004).

We should also note that increased dopamine concentrations in the nucleus accumbens do more than elicit reinforcing effects. One perspective suggests that enhanced dopamine signalling is related to latent inhibition effects. De Leonibus, Verheij, Mele, and Cools (2006) used microdialysis to examine nucleus accumbens dopamine levels in rats before and after introducing a novel or a familiar rat into the testing chamber. When the introduced rat was novel—that is, the experimental rat previously never met the introduced rat—dopamine levels increased in the nucleus accumbens. However, dopamine levels did not increase when familiar rats were introduced (**Figure 5.6**). In this way, dopamine may enhance the motivation to engage with novel stimuli or experiences.

Many drugs of abuse activate reward circuits, achieving dopamine elevations far above those produced by natural reinforcers. For example, the psychostimulant drugs cocaine and amphetamine directly enhance dopamine release from axon terminals in the nucleus accumbens. In doing so, they can elevate nucleus accumbens dopamine levels many times greater than those achieved by natural reinforcers and novel stimuli (Carboni, Imperato, Perezzani, & Di Chiara, 1989; De Leonibus et al., 2006; Hajnal et al., 2004; Sharp, Zetterstrom, Ljungberg, & Ungerstedt, 1987). Other abused substances may indirectly alter the activity of these dopamine pathways, such as by reducing GABA's inhibitory effects on mesolimbic dopamine neurons, as is the case with opioid drugs (van Zessen, Phillips, Budygin, & Stuber, 2012; Xiao & Ye, 2008) (more on this in Chapter 10). Rewarding effects may also be produced by activating glutamate receptors in the nucleus accumbens (Koob & Volkow, 2009; LaLumiere & Kalivas, 2008).

**FIGURE 5.6 Novelty and Dopamine Release**

The presentation of novel rats led to significant increases in nucleus accumbens dopamine levels, whereas the presentation of familiar rats did not increase nucleus accumbens dopamine levels.




Source: Adapted from De Leonibus, Verheij, Mele, and Cools (2006).

## Chronic Use of Abused Substances and Changes to Learning and Memory Systems

Acute administration of a drug of abuse produces reinforcing effects by activating reward circuitry, as described earlier. During chronic drug use, genetic factors come into play to alter the activity or growth of neurons in the reward system. In particular, rewarding substances cause the expression of a transcription factor called ΔFosB, which leads to the generation of more dendritic spines on GABA neurons that lead from the nucleus accumbens to the ventral tegmental area (the ones activated by $D_1$ receptors, as noted earlier). The greater density of dendritic spines on these GABA neurons provides more ways for the axon terminals to make synaptic connections to the GABA neurons (Robison & Nestler, 2011). During chronic use of abused substances, the enhanced synaptic connectivity overall diminishes excitatory inputs onto the GABA neurons, reducing the activity of these neurons (Grueter, Robison, Neve, Nestler, & Malenka, 2013). In turn, the diminished activity of these GABA neurons is expected to provide less inhibition of dopamine neurons in the ventral tegmental area that terminate in the nucleus accumbens. This is an example of a common occurrence we find throughout systems in the brain—namely that neurons experience enhanced activity as a result of receiving less inhibition. The term that refers to this situation is *disinhibition*, and if eavesdropping on neuroscientists puzzling over neurocircuitry, you'll very likely hear the term come up from time to time.

Chronic administration of an abused drug leads to changes in other brain systems, especially those involved in learning and memory. The interconnected structures that facilitate learning and memory include the amygdala, thalamus, prefrontal cortex, and hippocampus. Each of these structures adapts to the chronic use of abused drugs (**Figure 5.7**). Researchers who study the disease model of addiction refer to such structures to show how chronic use of substances causes long-lasting detrimental changes to physiological systems.

The amygdala is a structure traditionally associated with fear and anxiety, yet it also supports learning and memory by associating stimuli with emotional events, such as experiencing rewarding effects from a drug. During chronic drug use, the **amygdala** forms associations between stimuli commonly present during drug use and the reinforcing effects of the drug. The amygdala communicates this information to two other structures important for learning and memory.

First, the amygdala is interconnected with the thalamus, a structure that routes sensory information to the cerebral cortex. Second, the amygdala interconnects with the prefrontal cortex, the brain's executive center where stimuli are processed and motor responses are initiated. These structures together form the *thalamocortical-amygdala pathway*.

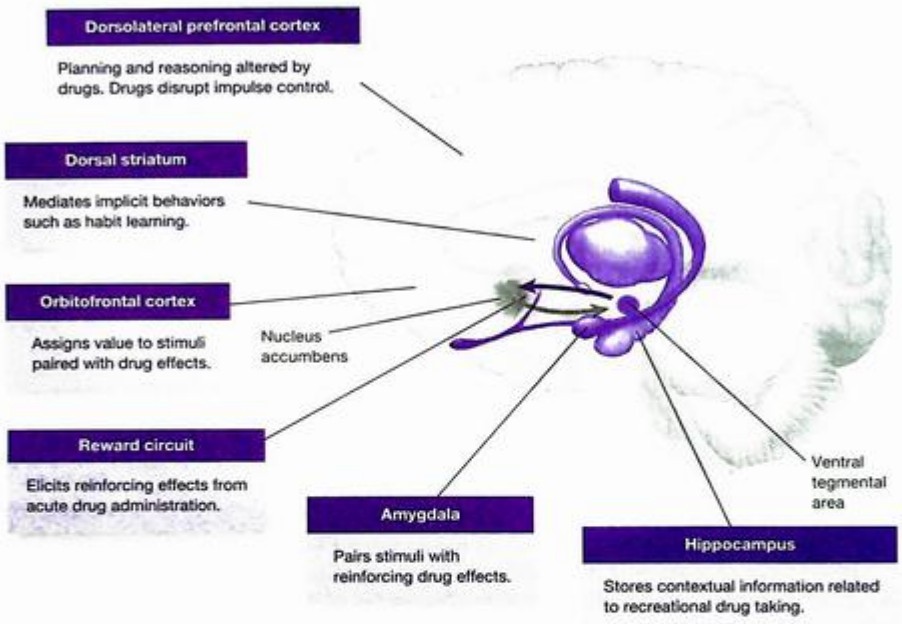
The prefrontal cortex contains substructures important for normal learning processes, and these structures adapt to chronic drug use. The **orbitofrontal cortex**, a structure within the prefrontal cortex, receives input from the amygdala and may enhance the incentive value of stimuli associated with drug use. The orbitofrontal cortex may also elicit drug cravings when the drug is absent (Koob & Volkow, 2009).

**Amygdala (role in drug addiction)**
During chronic use of an abused substance, associates stimuli commonly present during drug use with the reinforcing effects of the drug; elicits physical withdrawal symptoms and a negative emotional state when drug is absent

**Orbitofrontal cortex (role in drug addiction)**
A structure within the prefrontal cortex that receives input from the amygdala and may enhance the incentive value of stimuli associated with drug use; may elicit cravings when the drug is absent

**FIGURE 5.7 Brain Structures Involved in Addiction**

Chronic administration of abused drugs affects many brain structures beyond the reward circuit. Through incorporating these structures, chronic drug administration leads to pairing stimuli with drug effects, associating an environmental context with drug effects, and inhibiting impulse control and reasoning.




The thalamo-cortical-amygdala pathway also has connections with the hippocampus. During chronic administration of a drug of abuse, the hippocampus provides contextual information linked with drug taking. Examples of context include the physical environment where drugs are normally taken or the types of individuals a user interacts with when obtaining and administering drugs.

The structures described above play an important role in associating stimuli with drug effects and assigning value to these associated stimuli, such as conditioned reinforcing properties. *Conditioned place preference procedures* demonstrate these stimulus associations, as described in Box 10.1 in Chapter 10. In this procedure, laboratory animals are repeatedly exposed to an environment while experiencing a drug's reinforcing effects. As a result of these exposures, animals, when given the choice, develop a preference for being in the drug-associated environment. In fact, these environmental stimuli alone can elicit enhanced dopamine levels in

the nucleus accumbens (Duvauchelle, Ikegami, Asami, et al., 2000; Duvauchelle, Ikegami, & Castaneda, 2000).

In addition to a role in pairing stimuli with a drug's reinforcing effects, the amygdala-thalamo-cortical circuitry facilitates unpleasant drug withdrawal effects. Physical withdrawal effects manifest from the involvement of this circuitry with autonomic systems, particularly those involved with internal regulatory processes. The amygdala influences these functions through connections with the **hypothalamus**. During repeated administration, these systems adapt to a drug in the body; when the drug is absent, they elicit physical withdrawal symptoms such as decreased heart rate, gastrointestinal dysfunction, sweating, and breathing irregularities, among a variety of effects.

**Hypothalamus (role in drug withdrawal)**
Elicits autonomic system effects associated with physiological withdrawal symptoms

During withdrawal from a drug, we also find the amygdala reducing the activity of dopamine neurons in the ventral tegmental area (Belujon, Jakobowski, Dollish, & Grace, 2016). These inhibitory effects, in turn, reduce one's ability to experience rewarding effects. Thus, the amygdala elicits a negative emotional state, such as *anhedonia* (a lack of joy), as a form of psychological withdrawal.

Chronic administration of abused drugs also alters functioning of the dorsolateral prefrontal cortex. The **dorsolateral prefrontal cortex** integrates sensory information received from other cortical areas and mediates working memory, planning, organizing, and other upper-level cognitive activities. Through these activities, the dorsolateral prefrontal cortex is important for impulse control.

**Dorsolateral prefrontal cortex**
Integrates sensory information received from other cortical areas and mediates working memory, planning, organizing, and other upper-level cognitive activities; important for impulse control

Chronic use of an abused drug compromises normal functioning of the dorsolateral prefrontal cortex. Many drug-addicted individuals exhibit a reduced ability to choose delayed larger reinforcers in place of immediate smaller reinforcers. Overall, this behavior creates a problem for drug addiction therapy because delayed outcomes associated with being drug free may weigh poorly against immediate gratification from taking a drug of abuse. Other drugs, such as depressant drugs (e.g., alcohol) or psychedelic drugs (e.g., phencyclidine), significantly impair memory function, partly through acting on the dorsolateral prefrontal cortex (Aura & Riekkinen, 1999; Mao, Arnsten, & Li, 1999; Paulus, Tapert, Pulido, & Schuckit, 2006).

**Review!** Working memory consists of short-term verbal or nonverbal memories employed when carrying out a task (Chapter 2).

Chronic treatment with an abused drug may recruit procedural memory systems involving dorsal parts of the basal ganglia—also referred to as the *dorsal striatum*—and interconnections between this structure and the nucleus accumbens and thalamus. As Robinson and Berridge (2003) describe, tying shoelaces involves procedural memory because once lace tying starts, the behavior basically continues automatically until the lace is tied. During situations in which a user commonly smokes a cigarette, such as talking on the phone or having a cup of coffee, the user may engage in an automated series of behaviors involving removing a cigarette from a pack and lighting it. In other words, a user may obtain, light, and smoke a cigarette without giving it much thought.

## STOP & CHECK

1. What effects does dopamine release in the nucleus accumbens have?
2. What role does GABA play in the reward circuit?
3. What role does the amygdala play in chronic drug actions in the brain?
4. How might altered dorsolateral prefrontal cortex functioning interfere with treating addiction?

1. Enhanced dopamine concentrations in the nucleus accumbens are linked to reinforcing effects and may facilitate certain associative learning processes involving novel stimuli. 2. GABA neurons produce inhibitory effects on dopamine neurons in the reward circuit. 3. The amygdala pairs stimuli with a drug's reinforcing effects. 4. Compromised dorsolateral prefrontal cortex functioning impairs impulse control, which may prevent drug-addicted individuals from abstaining from immediate drug use in place of delayed benefits from being drug free.

## Neurobiology and the Stages of Drug Addiction

**Intoxication**
A drug's effects after acute administration that overall produce an abnormal and impaired state

Leading authorities in drug addiction research describe addiction as a cycle involving three primary stages (Kalivas, 2002; Koob & Volkow, 2009). The first stage of addiction is **intoxication**, a drug's effects after acute administration that produce a maladaptive and impaired state. The second stage is withdrawal, and the third stage consists of preoccupation and anticipation. These stages relate to important concepts developed from drug addiction models and their association with drug actions in the brain (**Table 5.4**).

*Drug intoxication* is a necessary first stage in the development of drug addiction. Drug use during this stage occurs for the purpose of achieving a drug's intoxicating and, in particular, rewarding effects. In this way, the intoxication stage resembles

**TABLE 5.4 Drug Addiction Cycle**

| Addiction Stage | Characteristics | Neurobiology |
|---|---|---|
| Intoxication | Acute drug effects that produce an impaired state | Reward circuitry |
| Withdrawal | Repeated drug use results in physical or psychological withdrawal effects (or both) | Amygdala, hypothalamus, and autonomic nervous system |
| Preoccupation and anticipation | Behavior orients from seeking natural reinforcers to drug seeking | Prefrontal cortex, amygdala, thalamus, and hippocampus |

the primary feature of Wikler's drive model as previously described. The actions of drugs on the brain's reward circuitry sufficiently explain drug use at this stage.

The next stage of this cycle consists of the *development of withdrawal during chronic use*. As drug use continues, the reasons for using the drug shift from purely seeking a drug's positive reinforcing effects to avoiding withdrawal effects. The opponent-process model characterizes this change in motivation for drug seeking, and we also note that due to allostasis, the effects produced by the drug, rather than a natural reward, are necessary to offset opposing processes. Neurobiologically, withdrawal effects depend largely on the amygdala. As previously described, the amygdala functions to pair stimuli with a drug's effects. When these drug effects cease, the amygdala, through connections with the hypothalamus and autonomic nervous system control centers such as the medulla, triggers an array of physical withdrawal symptoms. These physical withdrawal symptoms can include gastrointestinal effects, heart rate changes, breathing rate changes, body temperature dysregulation, and sleep disturbances. Further, the amygdala facilitates negative affective symptoms such as fear, anxiety, and dread. Although the amygdala is capable of producing a wide array of withdrawal effects, the specific withdrawal effects produced depend on the particular drug a person has been using.

As the chronic use of abused drugs continues, addiction enters a *preoccupation and anticipation stage*. During this stage, a person is preoccupied with seeking and using drugs. Drug use at this stage is more than simply seeking a drug for positive reinforcing effects or avoiding aversive withdrawal effects. Rather, this stage reflects a learning pattern of drug seeking that can conflict with learning patterns important for normal everyday activities. Incentivization of stimuli that promote drug "wanting" may develop through the intercommunication of brain reward circuitry with learning systems, including the thalamo-cortical-amygdala pathway and the hippocampus. Overall, this circuitry facilitates associating drug effects with stimuli, especially in assigning value to these stimuli. Through changes in the prefrontal cortex, chronic drug use affects planning and decision making, thereby facilitating a preoccupation with drug seeking and use. The global lasting impact drug addiction has wrought upon the brain at this stage also corresponds with the disease model of addiction.

Relapse represents another important feature of this third addiction stage. In a neurobiological context, relapse occurs as a result of the drug's changes to the brain's learning systems. In particular, encountering stimuli once strongly paired with drug use may elicit the desire for a drug by reengaging systems that facilitated drug seeking. Studies by Kalivas and colleagues show that such stimuli activate glutamate neurons that innervate the nucleus accumbens and ventral tegmental area (Kalivas, 2009; LaLumiere & Kalivas, 2008). These glutamate signals may reengage neural associations that gave incentive value to these stimuli, essentially eliciting a wanting state.

The stimuli that set off a pattern of behavior leading ultimately to relapse are more generally referred to as *triggers*. Those going through addiction treatment are advised to avoid such stimuli for these reasons, although the pervasive nature of conditioning with stimuli taking place during drug use makes this difficult. Both external and internal stimuli may prove as reminders of drug use. External stimuli

might consist of locations or people associated with use, drug paraphernalia, depictions of drug use, events that create stress or provoke memories of use, or engaging in activities that had generally led to or involved drug use. Internal stimuli might consist of negative feelings (e.g., sadness, anger, stress, anxiety); positive feelings (e.g., excitement, passion, celebratory); and boredom. Another trigger is the drug itself, which is the reason for many treatment programs advocating complete abstinence. Box 5.1 reviews a procedure used in lab animals to show the effectiveness of the substance itself reengaging drug-seeking behavior.

## Mortality and Drug Addiction

Once established, a drug addiction is long lasting and challenging to treat. Individuals who fail to respond to treatment have a high mortality rate compared to individuals who responded to treatment and remained drug free. A longitudinal study conducted by Mützell (1998) provides an assessment of mortality rates among treated and nontreated drug-addicted patients. Mützell conducted a 20-year longitudinal study of 284 heroin-addicted individuals. Those followed in the study had initially reported to an emergency room for heroin overdose. After receiving emergency care, medical staff invited these patients into a drug addiction treatment program. Among those electing to enter a program, more than half ceased treatment soon after.

Twenty years later, the researchers found that over two-thirds of the heroin-addicted individuals had died—regardless of whether or not they had attempted treatment at the hospital. The most frequent causes of death were pneumonia, suicide, physical assault, alcohol intoxication, heroin overdose, and cirrhosis of the liver. During those 20 years, two-thirds of the individuals had also committed various crimes. Only approximately 10 percent of the group had remained drug free. These results are similar to a longitudinal study conducted by Hser, Hoffman, Grella, and Anglin (2001) in the United States among individuals addicted to heroin or other opioid drugs. After a 30-year follow-up, approximately half had died; approximately half of those living, however, tested negative for drug use (Hser et al., 2001).

High mortality rates associated with drug addiction apply to legally available drugs as well. Long-term tobacco use is the greatest cause of deaths from lung cancer, chronic obstructive pulmonary disease, and heart disease annually in the United States. Alcohol causes thousands of U.S. deaths each year from liver diseases and alcohol overdose. Moreover, alcohol is a significant contributor to lethal car accidents and violence-related deaths each year.

## Psychological and Pharmacological Therapies for Treating Drug Addiction

Drug addiction treatment options include psychotherapy, medications, or a combination of both. These forms of treatment address drug detoxification, prevention of and coping with withdrawal symptoms, and the prevention of relapse. Detoxification is the first step in any addiction treatment.

**Detoxification** consists of a process aimed at ceasing drug intoxication and reducing withdrawal symptoms. Detoxification uses two key approaches: medication and prevention of drug use. Medications provide the means to reduce or eliminate short-term withdrawal symptoms. Otherwise, a drug-addicted individual may simply refrain from using a drug or be denied access to the drug. For a treatment program, detoxification from illicit substances usually occurs in a hospital setting or an in-house treatment facility.

**Detoxification**
Process aimed at ceasing drug intoxication and reducing withdrawal symptoms

After the completion of drug detoxification, treatment options seek to reduce further withdrawal symptoms and prevent relapse. Both medication and psychotherapy provide approaches for remaining drug free. Medications for treating drug addiction include those that directly address drug withdrawal symptoms and medications that treat comorbid disorders such as depression and anxiety. One medicinal approach is drug replacement therapy.

**Drug replacement therapy** exchanges the addictive drug with a similar but less harmful drug. For treating a heroin addiction, for example, medications can include substitute heroin-like drugs (such as buprenorphine or methadone) to prevent physical and psychological withdrawal symptoms. Replacement therapies for tobacco include nicotine patches, nicotine gums, and nicotine-like drugs such as *varenicline (Chantix)*. Treating drug addiction using the drug replacement approach requires that an individual slowly reduce the amount of replacement substance used until the individual can successfully quit without the occurrence of appreciable withdrawal symptoms.

**Drug replacement therapy**
Exchanging the addictive drug with a similar but less harmful drug

Another approach consists of psychotherapy. For drug addiction, *psychotherapy* includes behavioral therapies and cognitive-behavioral therapies. Each therapy type seeks to eliminate maladaptive behavior surrounding drug use. Toward this goal, therapy aims to reduce addictive drug use to manageable levels or to eliminate drug use altogether.

**Cognitive-behavioral therapies** teach drug-addicted individuals to identify and reduce their urges to use a substance. Once trained, individuals learn to avoid stimuli or situations that precipitate drug cravings and learn strategies for coping with drug cravings. For legal substances such as tobacco and alcohol, cognitive-behavioral therapy goals may consist of reduced and responsible drug use rather than completely ending drug use. In this perspective, addictive drug use is a manageable behavior, not an incurable disease.

**Cognitive-behavioral therapies**
Therapies that teach drug-addicted individuals to identify and reduce urges to use a substance

Twelve-step recovery programs such as Alcoholics Anonymous and Narcotics Anonymous are common social therapies for drug addiction. Although they are conducted in a group setting, we do not consider these programs to be group psychotherapy because the group leader may not be a trained or licensed therapist and psychotherapy techniques are not used. Instead the group leader is generally an individual who has succeeded in the 12-step program and can use his or her knowledge and experiences in the program to run group meetings. Thus, the "therapy" in this context consists of individuals sharing with others their struggles and successes in a supportive group setting.

These programs tend to characterize drug addiction similar to a disease model; that is, drug addiction is something inherent and lifelong. These programs advocate complete abstention from substance use to prevent drug addiction from recurring.

From this perspective, we term someone successfully abstaining from substance use for a long period of time as "in recovery," similar to someone in recovery from a disease. The term used in this context also highlights the belief that no one can ever be "cured" of drug addiction, that a relapse is always possible.

**Twelve-step anonymous programs**
A type of substance addiction program where anonymous members give testimonies in group settings and follow an outline of 12 steps toward recovery

**Twelve-step anonymous programs** guide members, known only on a first-name basis, through 12 recovery steps, beginning with an admission that drug use is out of control. The 12 steps further include acceptance of weaknesses in control of drug use as well as other parts of their life. Ultimately, these weaknesses are addressed through moral and social support by group members, a program sponsor, and family and friends. Twelve-step programs also encourage members to accept a greater moral purpose or power beyond themselves, which contributes to a heightened sense of spirituality.

Although a variety of treatment options exist, all have relatively low success rates. A nationwide assessment of treatment effectiveness called the Drug Abuse Treatment Outcomes Study provides one of the best surveys of long-term outcomes of drug addiction treatment. This study assessed the effectiveness of four primary treatment programs for patients who abused heroin, cocaine, marijuana, or alcohol. The programs consisted of outpatient methadone treatment, long-term residential treatment, outpatient drug-free treatment, and short-term inpatient treatment. Both long-term residential and short-term inpatient treatments employed some type of medication to address cravings or physiological withdrawal effects. Outpatient drug-free treatment programs provided any variety of therapeutic approaches, including 12-step programs or one-on-one therapy. Short-term inpatient programs provided some type of medical treatment to address symptoms derived from abrupt withdrawal of a drug.

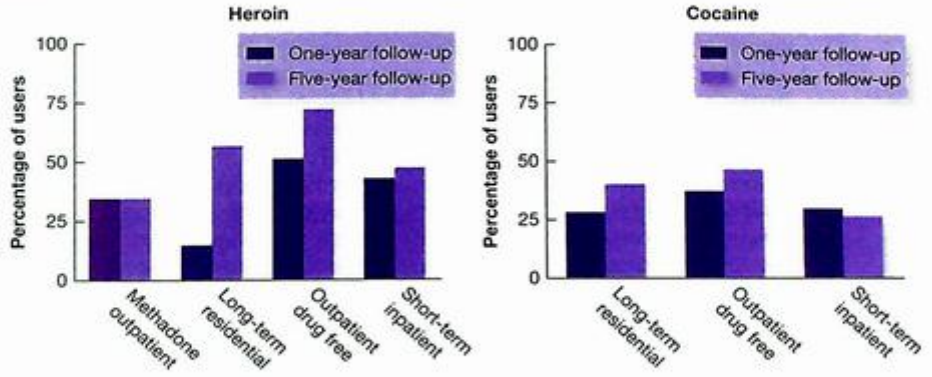
Although most patients reported declines in substance use one year later, a follow-up with patients five years later revealed increased trends in substance use (Hubbard, Craddock, & Anderson, 2003) (**Figure 5.8**). More individuals previously enrolled in methadone outpatient and long-term residential treatment programs for heroin abuse reported using heroin at a five-year follow-up compared to a one-year follow-up. The number of individuals previously enrolled in a long-term residential treatment or outpatient program for heroin or cocaine use also increased when surveyed five years after treatment compared to one year after treatment. Fortunately, not every program saw increased relapse rates. While five-year follow-ups found a slight increase in heroin use for a short-term inpatient program, there was also a slight decrease in cocaine use for short-term inpatient programs.

Although increased substance use was reported for two programs shown in Figure 5.7, many patients had relapsed and then sought treatment again during this five-year period. To determine why some patients sought treatment again after relapse but others did not in the Drug Abuse Treatment Outcomes Study, Grella, Hser, and Hsieh (2003) conducted an analysis of the reasons patients expressed for re-seeking treatment.

For this analysis, Grella and colleagues (2003) focused on cocaine-addicted users who relapsed during this study. By assessing the data gathered on these users, this research team used correlational study procedures to determine the impact of certain personal or environmental characteristics on the decision to re-seek treatment. The investigators found that users re-seeking treatment after relapse

**FIGURE 5.8 Treatment Program Outcomes for Heroin and Cocaine Addiction**

One-year (solid bars) and five-year (shaded bars) follow-ups in patients seeking a treatment for heroin (left) or cocaine (right) addiction. The bars report the percentage of patients still using a substance for each program.




Source: Adapted from Hubbard et al. (2003).

had an increased likelihood of being married and had past experiences with drug treatment programs. Among these prior treatment programs, most users who re-sought treatment had participated in a 12-step recovery program. Finally, those re-seeking treatment expressed a desire for help and a readiness to accept treatment. Findings such as these provide researchers and therapists directions for improving successful treatment approaches.

## STOP & CHECK

1. Which neurobiological systems mediate rewarding effects during the intoxication of drug use?
2. How do withdrawal symptoms occur when a chronically administered drug is absent from the body?
3. What is the first step in addiction treatment?
4. What is the key difference between behavioral or cognitive-behavioral therapies and 12-step programs such as Alcoholics Anonymous?

1. The reward circuit structures, which consist of the ventral tegmental area and the nucleus accumbens 2. When an addicted drug is absent, the amygdala elicits a negative affective state and elicits the hypothalamus to produce autonomic nervous system effects, leading to withdrawal symptoms. 3. Detoxification 4. Behavioral and cognitive-behavioral therapies seek to reduce drug use to a manageable level. Anonymous programs seek the complete abstinence of the addicted drug's use.

## From Actions to Effects: Food Addiction

*Food addiction* shares many features with drug addiction. Food addiction appears to be relatively prevalent among maladaptive disorders. Although we lack precise numbers on the prevalence of food addiction, currently one-third of U.S. adults have body mass index (BMI) values over 30, which is the medical definition for *obesity*. Obesity in the United States accounted for more than $200 billion in health care expenses between 1998 and 2000, and obesity contributes to more than 300,000 deaths in the United States each year. Although obesity occurs from many factors, including physical inactivity, types of foods consumed, and genetic predispositions, the rewarding effects of highly palatable foods are likely contributors.

However, overeating in food addiction may not necessarily equate to obesity. Bulimia nervosa is an eating disorder characterized as binge eating followed by a compensatory response to avoid gaining weight. The compensatory response may consist of vomiting, using laxatives, overexercising, or any of a variety of different methods to prevent gaining weight from overeating. Binge eating typically involves sweet-tasting, high-calorie foods, which suggests that bulimia nervosa can be considered a form of food addiction (Hadad & Knackstedt, 2014).

Food addiction is an emerging focus for mental health professionals. The current DSM does not characterize food addiction as a disorder, per se, but clinicians who work with food-addicted individuals tend to follow criteria used for diagnosing a substance use disorder (Davis et al., 2011; Ifland et al., 2009). Further, we find growing scientific interest in considering habitual overeating to be similar to substance use disorders (Ifland et al., 2009; Volkow & O'Brien, 2007; Volkow & Wise, 2005). Here, we consider some of the features that food addiction shares with substance use disorders.

A study by Pretlow (2011) provides an illustration for how obesity might satisfy DSM criteria for a substance use disorder. This study relied upon the earlier edition of the DSM, the DSM IV-TR, but the major features of substance use disorders relevant to their study are the same for the most current DSM, the DSM-5. This study included a survey of anonymous qualitative statements provided by nearly 30,000 individuals ranging from age 8 to 21. All participants had BMI levels 30 or higher and were, on average, at the 96th percentile for BMI.

From reviewing statements posted on the study's website, Pretlow wrote that "the majority of posts exhibited at least three criteria [for substance use disorders], particularly: (a) large amounts of substance consumed over a long period, (b) unsuccessful efforts to cut down, and (c) continued use despite adverse consequences." Further, participants described food use that shared many characteristics of drug tolerance, which consisted of progressively increasing food consumption over time, and drug withdrawal, as characterized by urges to overeat when attempting to diet. Among those who reported urges, nearly half described them as "intense cravings."

Overeating shares many of the neurobiological features of drug addiction (Hadad & Knackstedt, 2014; Volkow, Wang, Fowler, Tomasi, & Baler, 2012). Like drugs of abuse, foods can produce reinforcing effects by acting on brain reward circuitry. As described previously, sugary liquid food consumed by rats causes large elevations in nucleus accumbens dopamine levels (Figure 5.3). Also, animal studies find increased levels of ΔFosB in the nucleus accumbens after a diet rich in sugar (Sharma & Fulton, 2013; Wallace et al., 2008). Appetite hormones also regulate dopamine neurons in the

reward pathway. The hunger-stimulating hormone ghrelin greatly enhances food-elicited increases in mesolimbic dopamine neuron activity, and therefore appears important for the rewarding value of food. Beyond this, ghrelin plays a role in the rewarding effects of addictive substances, such as alcohol and cocaine (Dickson et al., 2011). For example, research presented in Box 5.1 shows that ghrelin enhances self-administration responding for heroin. The hunger-reducing hormone leptin diminishes food-elicited increases in dopamine neuron activity. Thus, hunger enhances food's reinforcing effects, whereas satiety reduces food's reinforcing effects.

Food addiction therapies resemble drug addiction therapies. Cognitive-behavioral approaches attempt to alter a person's view of food and then develop strategies to cope with food cravings. Just as 12-step programs include Alcoholics Anonymous and Narcotics Anonymous, 12-step groups exist for overeating, such as Overeaters Anonymous and Food Addicts Anonymous (Johnson & Sansone, 1993; Russell-Mayhew, von Ranson, & Masson, 2010). However, unlike most strategies for drug addiction, one cannot abstain from food, and therefore, strategies focus on avoiding highly-palatable foods and controlling the degree of intake of food. Also like drug addiction, similar triggers can lead to relapse (Parylak, Koob, & Zorrilla, 2011).

Medically, however, most therapies address the physical impact of food addiction rather than treating the addiction itself. For example, medical obesity treatments include appetite-reducing medications, medications that impair food absorption, and surgical procedures (Powell, Apovian, & Aronne, 2011; Stefater, Wilson-Perez, Chambers, Sandoval, & Seeley, 2012). Surgical procedures include liposuction, a fat-extracting procedure, and stomach bands or staples, which reduce the size of the stomach.

Otherwise, the DSM considers overeating, or *compulsive eating*, as a symptom of another disorder, such as anxiety or depression. Thus, to reduce overeating, one must treat the disorder causing overeating. For example, if overeating is a way of coping with stress or anxiety, then directly treating stress or anxiety will reduce overeating. Similarly, if overeating allows one to cope with depression, then treating depression will reduce overeating.

Thus, although psychologists and other mental health therapy providers treat overeating either as a substance use disorder or as a symptom of another disorder, the lack of a clear clinical definition for food addiction leaves food-addictive behaviors largely in the realm of medical symptoms for other disorders. An agreement among mental health professionals about food addiction would help clarify this diagnosis and aid in the development of appropriate treatment strategies.

## STOP & CHECK

1. How do highly palatable foods elicit reinforcing effects?
2. How do therapists diagnose food addiction?

1. Like drugs of abuse, foods elicit increased dopamine release in the nucleus accumbens. 2. The DSM does not include food addiction among psychological disorders. However, therapists find that the general DSM definition for a substance use disorder applies as well to food addiction. Moreover, some therapeutic approaches for drug addiction, such as 12-step programs, also apply well to food addiction.

## CHAPTER SUMMARY

Regulatory agencies regulate the availability and use of drugs with abuse potential. In the United States, the Drug Enforcement Administration categorizes such drugs according to abuse potential and medical utility on a controlled substances schedule. Drug scheduling occurs in other countries, but their methods and category systems sometimes differ. Although drug scheduling provides a regulatory rating for the abuse potential of drugs, these ratings do not necessarily coincide with scientific ratings of abuse potential. Clinical definitions of drug addiction include harmful effects from drug use and consider addiction as a chronically relapsing disorder.

To understand addictive behavior better, researchers use drug addiction models. These models include considering addiction as a disease or as behavior controlled by drug-elicited variables. Drugs of abuse derive their effects through acting on the brain's reward circuit, which was first discovered by James Olds. Drugs that elicit positive reinforcing effects cause dopamine neurons in the reward circuit to release dopamine into the nucleus accumbens. Chronic usage of drugs of abuse affect brain structures for learning and memory.

We have many treatment strategies for addiction, including detoxification, medicines, and therapy—unfortunately, these strategies offer limited success. Many of the features of drug abuse and addiction relate to other addictions as well. For example, food addiction engages many of the same brain systems involved in drug addiction, satisfies clinical definitions for drug addiction, and can be treated by many approaches used for drug addiction.

## KEY TERMS

Harrison Narcotics Act 130
Controlled Substances Act 130
Controlled substances schedules 130
Craving 133
Relapse 134
Models of drug addiction 134
Associative learning 135
Reinforcement 135
Conditioned stimulus 135
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## A FINAL NOTE ABOUT DRUG ADDICTION

If you or someone you know may be struggling with addiction, please consider looking into any of the following resources.

1. Most colleges can refer students to addiction services. Consider contacting your institution's health center or contacting a substance abuse awareness office on your campus. You might find a listing of resources on your college's website as well.
2. The National Council on Alcoholism and Drug Dependence offers a free online self-assessment to help you determine if you might have a drug addiction. You can find the test here: https://ncadd.org/get-help/take-the-test/am-i-drug-addicted. For seeking help with addiction, this organization's phone number (U.S.) is 800-622-2255.
3. The U.S. Substance Abuse and Mental Health Services Administration offers a source for locating treatment services. You can call their helpline at (U.S.) 800-662-4357 or visit their online treatment services locator at https://findtreatment.samhsa.gov.
4. Contact your county's department of health. Most can refer you to drug addiction treatment services.
5. Searching for a particular 12-step program (e.g., Alcoholics Anonymous) in your town on an Internet search engine is a quick way to find where and when these groups meet.

CHAPTER 6

# Psychostimulants

## Chapter Outline

- Psychostimulants: Herbal Products, Prescription Drugs, and Substances of Abuse
- Pharmacokinetics of Psychostimulants
- Psychostimulants and Monoamine Neurotransmitters
- Pharmacological Effects of Psychostimulants
- From Actions to Effects: Psychostimulants as Cognitive Enhancers and Treatments for ADHD

## Learning Objectives

- Describe the types of psychostimulant substances
- Characterize the manner of use of psychostimulants according to pharmacokinetic actions
- Describe the pharmacological actions of psychostimulants
- Describe the pharmacological effects of psychostimulants
- Understand the features and treatments of psychostimulant addiction

Throughout the day, all of us experience moments of high alertness and arousal. You might experience this after realizing you slept through your alarm clock and have to rush out the door to avoid being late. Or, you might be jolted to alertness if a car swerves in front of you, and you quickly slam on the brakes. You may become more attentive if your instructor begins randomly choosing students in class to answer questions about the lecture she just gave.

Think about how you feel in these situations. Your heart rate probably becomes rapid. Your mind is racing to meet the challenge you face. You are in a state of high alertness. You might even find the experience exhilarating. All of these states activate arousal processes in the central and peripheral nervous systems. Psychostimulant drugs act on these same nervous system processes.

**Psychostimulants**
Drugs that increase psychomotor and sympathetic nervous system activity as well as improve alertness and positive mood

**Psychostimulant drugs** increase psychomotor and sympathetic nervous system activity as well as improve alertness and positive mood. Psychostimulants are also referred to as *sympathomimetics*, because they increase sympathetic nervous system activity. Common psychostimulants include amphetamines, methylphenidate, cathinones, cocaine, and modafinil. Amphetamines represent a class of drugs, among which are amphetamine and methamphetamine. Cathinones include many drugs, such as cathinones and pyrovalerone, as well as synthetic cathinones.

Although psychostimulants are common drugs of abuse, many psychostimulant drugs have legitimate therapeutic purposes. Some amphetamines are prescribed for the treatment of *attention deficit hyperactivity disorder* (ADHD), narcolepsy, and obesity. Cocaine was once commonly used as a local anesthetic for nasal and tear duct surgery. Given these medical uses, the U.S. Drug Enforcement Administration (DEA) assigns most psychostimulant drugs above schedule I (see **Table 6.1**). However, the level of regulatory control for these drugs varies among countries. Canada, for example, assigns methamphetamine to schedule I, thereby preventing medicinal use of methamphetamine.

Many types of psychostimulants are well known as drugs of abuse. In the United States, the Department of Health and Human Services conducts annual national surveys (taken anonymously) to assess the degree of illicit drug use among those 12 or older. According to this survey, 5.4 percent of Americans have used methamphetamine in their lifetime, 14.9 percent of Americans have used cocaine, and 3.3 percent of those Americans have used the "crack" form of cocaine (Substance Abuse and Mental Health Services Administration, 2017). In Europe, 5.4 percent of those 15 and

**TABLE 6.1** **Drug Enforcement Administration Controlled Substances Schedules for Psychostimulant Drugs**

| Psychostimulant | Schedule |
|---|---|
| Amphetamine | III |
| Cathinone | I |
| Cathine (norpseudoephedrine) | IV |
| Cocaine | II |
| Methamphetamine | II |
| Methcathinone | I |
| Methylphenidate | II |
| Pyrovalerone | V |

*Source:* Adapted from the DEA Controlled Substances Schedules, www.deadiversion.usdoj.gov/schedules/index.html

older report using cocaine at some point in their lifetimes (European Monitoring Centre for Drugs and Drug Addiction, 2019). Nonmedical use of psychostimulants such as methylphenidate, amphetamine, and methamphetamine was reported by 1.6 million Americans, including 569,000 who used methamphetamine (Center for Behavioral Health Statistics and Quality, 2018). Among high school students in the United States, 1.1 percent reported using synthetic cathinones at least once during the past year (Palamar, 2015). Reports of synthetic cathinone use and overdose began appearing in 2010 and 2011 (CDC, 2011b; James et al., 2011; Wood, Greene, & Dargan, 2011), and bath salt ingredients not scheduled at the time received schedule I status soon after.

## Psychostimulants: Herbal Products, Prescription Drugs, and Substances of Abuse

### Ephedra

**Ephedra (or ma huang)** An extract of the plant *Ephedra sinica* that contains ephedrine and pseudoephedrine

The first amphetamines were derived from **ephedra** (also known as **ma huang**, translated as "hemp yellow"), primarily found as an extract of the plant *Ephedra sinica* grown naturally in dry climates in North and Central America, southern Europe, and Asia (**Figure 6.1**) (Abourashed, El-Alfy, Khan, & Walker, 2003; Lee, 2011). We find documented use of ephedra as a medicinal herb for the treatment of cough, reduction of fever, induction of sweating, and generally as a stimulant in sixteenth-century China (Lee, 2011). Ephedra contains two psychostimulants: *ephedrine* and *pseudoephedrine* (**Table 6.2**), both of which were first isolated by the Japanese chemist Nagayoshi Nagai in 1885 (Lee, 2011). Ephedrine and pseudoephedrine

**TABLE 6.2 Psychostimulants**

| Psychostimulant | Related Psychostimulants | Origin |
|---|---|---|
| Ephedrine | | Both ephedrine and pseudoephedrine derive from *Ephedra* |
| | Pseudoephedrine | |
| Amphetamine | | Laboratory synthesis |
| | Methamphetamine | From ephedrine or pseudoephedrine |
| Methylphenidate | | Laboratory synthesis |
| Cathinone | | The *khat* plant |
| | Methcathinone | Synthesized from cathinone |
| | Mephedrone | Synthesized from cathinone |
| | Methylone | Synthesized from cathinone |
| | Methylenedioxypyrovalerone (MDPV) | Synthesized from cathinone |

**FIGURE 6.1** ***Ephedra sinica***

*Ephedra sinica* plants are native to dry climates in North and South America, southern Europe, and Asia.

Copyright iStockphoto/Renphoto

**Alkaloid**
Plant-derived physiologically active organic compounds that contain nitrogen

serve as examples of **alkaloids**, plant-derived physiologically active organic compounds that contain nitrogen. Many cold remedies contain these stimulants. In the United States, states limit the number of products sold in a single purchase in an effort to reduce the clandestine production of methamphetamine and other illicit psychostimulant drugs.

## Amphetamines

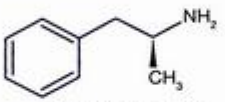
**Amphetamines** represent a class of psychostimulant drugs that share a similar structure (**Figure 6.2**). The drug amphetamine has two *optical isomers*—that is, the chemical structure occurs in two different forms that are *mirror images* of each other—designated as *d* or *l*.[1] The drug amphetamine (*Benzedrine*) refers to **racemic** amphetamine, a mixture containing equal amounts of both *d* and *l* optical isomers. The d-amphetamine isomer is sold as the medication *Dexedrine*, and the drug *Adderall*

**Amphetamines**
Class of psychostimulant drugs that share a similar structure

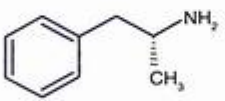
**Racemic**
A mixture containing equal amounts of both optical isomers of a compound

**FIGURE 6.2 Chemical Structures of Selected Amphetamines**

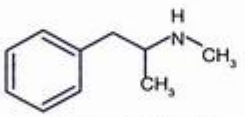
Amphetamines consist of psychostimulant drugs with similar chemical structures. The drug "amphetamine" comes in two optical isomers—d-amphetamine and l-amphetamine—that is, mirror images. For d-amphetamine, the solid cone connected to $CH_3$ represents this portion of the molecule pointing upward, whereas for l-amphetamine, the dashed lines connected to $CH_3$ represents this portion of the molecule pointing downward. We find a similar structure for methamphetamine—the "meth" in methamphetamine refers to the methyl ($CH_3$) chemical group shown attached to NH. Also shown in the figure is the mixed psychedelic and psychostimulant drug 3,4-methylenedioxy-N-methamphetamine, referred to as MDMA or by street names such as "ecstasy." We cover MDMA in Chapter 12, but its stimulant effects likely derive from having "methamphetamine" as part of its chemical structure.



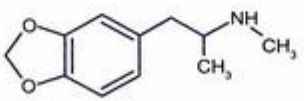

**D-amphetamine**




**L-amphetamine**




**Methamphetamine**




**3,4-methylenedioxy-N-methamphetamine (MDMA, also known as "ecstasy")**

[1]The *d* and *l* designations refer to dextrorotatory and levorotatory, meaning the molecules turn to the right or left in a plane of polarized light.

contains a 3:1 ratio of d-amphetamine and l-amphetamine. At one time, both racemic and d-amphetamine were approved by the Food and Drug Administration (FDA) for the treatment of attention deficit hyperactivity disorder and narcolepsy, but currently, these drugs have been pulled from the market. *Adderall*, however, remains on the market and has been approved by the FDA for the treatment of attention deficit hyperactivity disorder and narcolepsy (Food and Drug Administration, 2007). In addition, a related form of amphetamine, lisdexamfetamine (*Vyvanse*), is used for the treatment of ADHD.

Although methamphetamine is notoriously known as a drug of abuse, the FDA approves its use for the treatment of ADHD, marketed under the trade name *Desoxyn*. The illicit production of methamphetamine, however, occurs in a "meth lab," which uses household chemicals along with either ephedrine or pseudoephedrine. In addition, meth labs may use the chemical phenylacetone (or P2P) in place of either ephedrine or pseudoephedrine. Meth lab synthesis methods produce a crystallized form of methamphetamine referred to as *crystal meth*, *crystal*, *speed*, *crank*, and other street names (**Figure 6.3**). Synthesizing methamphetamine from these methods produces toxic and flammable solvent vapors and gases, which account for a large number of third-degree burn victims in emergency care every year.

German chemists developed amphetamine in 1887 in an effort to develop a mass-producible form of ephedra. In the 1920s, physicians used amphetamine as a

**FIGURE 6.3** **Methamphetamine Crystals**

Methamphetamine crystals are clandestinely made in meth labs from ephedrine, pseudoephedrine, or the organic solvent phenylacetone.

Department of Justice

drug for raising blood pressure; in 1937, amphetamine was first used to treat ADHD (Bradley, 1937; Brecher, 1972). Amphetamine's stimulant effects provided the first effective treatment for *narcolepsy*, a neurological sleep disorder characterized by extreme fatigue and excessive daytime sleep. During World War II, the U.S. military used amphetamine to improve alertness and reduce fatigue. After the war, leftover amphetamine supplies released to the general population led to a brief amphetamine abuse epidemic in Japan (Brecher, 1972; Brill & Hirose, 1969).

In 1919, Akira Ogata, a Japanese chemist, discovered methamphetamine after testing different synthesis methods that employed either ephedrine or pseudoephedrine. Another method was later developed for synthesizing methamphetamine from the organic solvent phenylacetone. In an attempt to reduce illicit methamphetamine production, the U.S. Drug Enforcement Administration first regulated the sale of phenylacetone, but this led illicit meth labs to synthesize methamphetamine from ephedrine or pseudoephedrine instead. In response to this, in 2006 the DEA began regulating the sale of ephedrine and pseudoephedrine, which, as described earlier, are common ingredients in over-the-counter cold medications (Vearrier, Greenberg, Miller, Okaneku, & Haggerty, 2012).

## Methylphenidate

*Methylphenidate* is a prescription psychostimulant drug used for the treatment of ADHD. Methylphenidate structurally differs from the amphetamines and cocaine and is available only in prescription form. We generally regard methylphenidate as a relatively weaker psychostimulant drug. To use methylphenidate as a drug of abuse, users may often obtain methylphenidate from instrumental users, that is, those who were prescribed methylphenidate for a legitimate medical use. Those who are prescribed methylphenidate may choose to recreationally use the drug by grinding it up and snorting it.

Methylphenidate was discovered in 1944 by Leandro Panizzon, a chemist working for the Ciba Pharmaceutical Company. Panizzon named the drug *Ritaline* after his wife Rita. After identifying the drug's psychostimulant effects, physicians began prescribing methylphenidate for the treatment of ADHD in the 1960s. However, ADHD was not universally accepted as a disorder until the 1980s, and as ADHD diagnoses subsequently increased, so did methylphenidate prescriptions. Today, methylphenidate is prescribed to more than two-thirds of the approximately five million U.S. children with ADHD (Mayes, Bagwell, & Erkulwater, 2008).

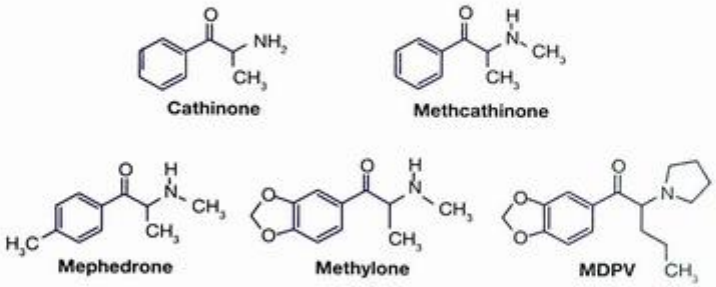
## Cathinones

**Cathinone**
Psychostimulant derived from the leaves of *Catha edulis*

The psychostimulant **cathinone** comes from the leaves of *Catha edulis*, which is also referred to as *khat*. It is found in east Africa and the Arabian Peninsula, and the traditional use of khat involves chewing the leaves or using the leaves in tea. Fresh khat leaves produce the most potent psychostimulant effects, which limits khat use to local inhabitants. A number of laboratory-synthetized cathinone compounds designed around cathinone's structure include methcathinone, methylenedioxypyrovalerone (MDPV), methylone, and mephedrone (Table 6.2, **Figure 6.4**).

**FIGURE 6.1 Chemical Structures for Cathinone and Synthetic Cathinones**

The chemical structure of cathinone (top-left) is shown along with synthetic cathinones, which share structural similarities with cathinone.




Synthetic cathinones make up approximately 25 percent of all new psychoactive drugs worldwide (United Nations Office of Drugs and Crime, 2014). We find the compounds sold by a variety of names, including "bath salts" or "plant food," and such concoctions can contain one or multiple types of synthetic cathinones (Baumann et al., 2012; Underwood, 2015). Synthetic cathinones packaged as bath salts are known by many names, including *Starry Nights, Vanilla, Sky,* and *White Rush* (**Figure 6.5**).

Inhabitants of Arabia, Ethiopia, and east Africa have used khat, the source of cathinone, for centuries. The first cultivation of khat was documented in the early 1300s by King Sabr ad-Din of Ifat, who ordered its planting in the town of Marad. Europeans first discovered khat during an expedition in 1760 to Arabia ordered by King Frederick V of Denmark. During this expedition, physician and botanist Peter Forsskål discovered khat and named the plant *Catha edulis* (Al-Hebshi & Skaug, 2005; Gebissa, 2010). Methcathinone was synthesized in the Soviet Union in 1928 and has been recreationally used since the late 1970s. Reports of methcathinone abuse began in the early 1990s (Emerson & Cisek, 1993; Glennon, 2014).

## Cocaine

**Cocaine**
Psychostimulant derived from the leaves of *Erythroxylon coca*

**Coca paste**
Liquid paste made from the breaking and mixing of coca leaves

Leaves of the *Erythroxylon coca* plant, which is found in the higher elevations of South America, provide a direct source of **cocaine** (**Figure 6.6**). The separation of cocaine from coca leaves occurs through multiple steps. The process begins by breaking down and mixing coca leaves into a liquid to form a **coca paste**. The coca paste, which contains between 30 and 80 percent of cocaine base, is then dried and sold for recreational use as is or transported to a *crystal lab* for further processing (Casale & Klein, 1993).

Crystal labs convert cocaine from a base into a salt, which puts cocaine in a powdered form. The salt form is produced for two reasons. First, it is a purer cocaine

**FIGURE 6.5** **Synthetic Cathinones Sold as "Bath Salts"**

We find synthetic cathinones sold as "bath salts," which are sold by many names, including *Starry Nights, Vanilla, Sky,* and *White Rush.*

product than the cocaine in extracted base form. Second, the salt form allows for either *insufflating* (snorting) or intravenously injecting cocaine.

Many cocaine users, however, prefer the base form, which can be smoked because it has a lower vaporization point. Vaporization of the salt form of cocaine occurs at a very high temperature: 195°C (383°F). This method makes it hard not only to reach these temperatures with an ignition source but also for users to safely inhale the vapors without burning themselves. However, the base form of cocaine has a lower vaporization point, 98°C (208°F), allowing users to easily smoke it by heating the crystals over a flame.

Given that smugglers often transport the salt form of cocaine, smoking cocaine requires transforming the salt form into a base form, also called a **freebase**[2]. This process consists of removing a hydrochloride molecule (the salt) from the cocaine molecule. When cocaine salt is heated with a mixture of baking soda and water, the hydrochloride molecule separates from cocaine, "freeing" the base from the salt.

**Freebase**
A base form of a compound converted from a salt form of the compound

**FIGURE 6.6 Cultivation and Production of Cocaine**

Cocaine is a constituent in the leaves of the *Erythroxylon coca* plant, which is found at higher elevations in South America. Workers cultivate coca plants (left) in order to make a coca paste (right), a first step in extracting cocaine from coca leaves.

Shutterstock/Rafaela Asprino

Department of Justice

The *freebase* form of cocaine is called *crack* cocaine because of the crackling sound these freebase crystals make when heated (**Figure 6.7**). The term *freebasing* refers to the process of converting a drug from a salt form to a base form and can also refer to using the freebase form of a substance. The term mostly applies to processing an illicit substance.

*Erythroxylon coca* was long used by indigenous people for religious purposes, appetite suppression, and enhanced vigor and stamina. In the mid-1500s, Spanish conquistadors first discovered the plant during their conquest of the Incan empire in Peru. Cocaine was first extracted from coca leaves in 1844. In 1883, Theodor Aschenbrandt, a German Army physician, reported the anti-fatiguing properties of cocaine in soldiers. This report inspired a young physician, Sigmund Freud, to study cocaine's behavioral effects (Freud, 1974).

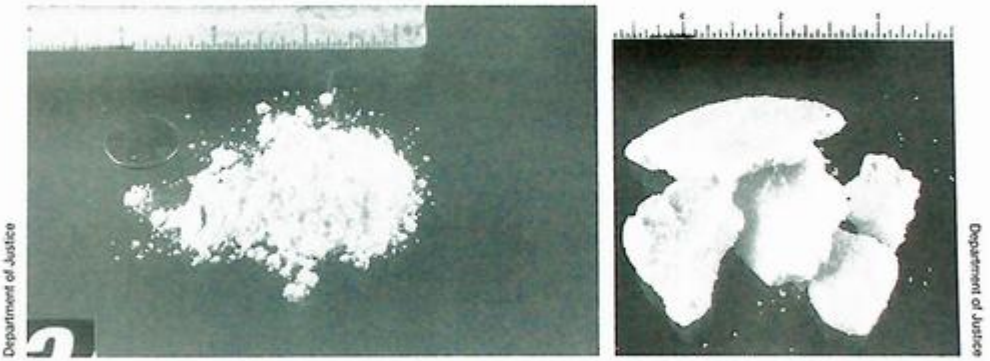
In 1884, Freud was fresh out of medical school and serving as a physician and lecturer at the Psychiatric Institute of the General Hospital of Vienna. Freud already had achieved a distinguished series of accomplishments in research on the nervous system. In fact, he wrote extensively in letters to his fiancée, Martha Bernays, about his desire for a career in research, but practicing medicine seemed his only option for making a living. He first chose to practice surgery because this required the least amount of interaction with his patients. A few months later, Freud obtained a psychiatric institute position, which held possibilities for research. A major discovery, he hoped, would lead to a profitable research career.

With this in mind, Freud sought a major discovery. He was intrigued by Aschenbrandt's reports on cocaine and decided to study it. In April 1884, Freud requested 1 gram of cocaine from Merck pharmaceuticals, and on June 18, 1884, less than two months later, he had completed both his research and a full manuscript on his findings.

In this manuscript, *Über Coca* ("On Coca"), Freud provided the most in-depth review of cocaine at the time, which included information on coca plants, ancient

**FIGURE 6.7 Forms of Cocaine**

Cocaine is used in both a powdered salt form (left) and a crystal or *crack* form (right).



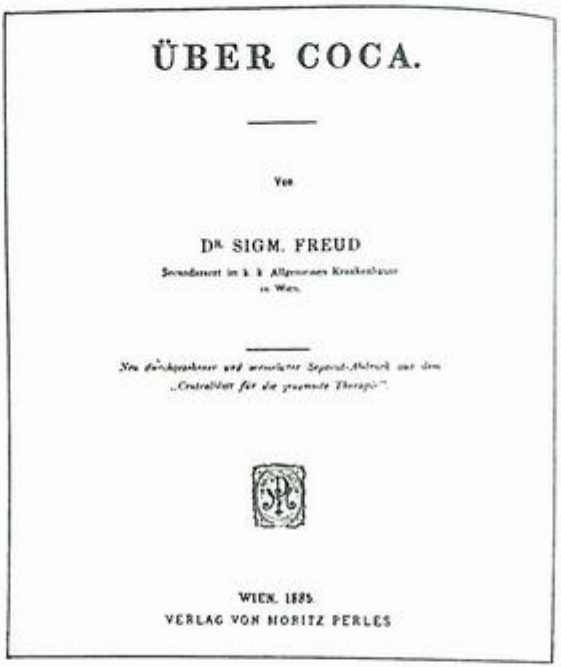

human use, effects observed in animals, and his own self-reports (**Figure 6.8**). Freud lauded the benefits of cocaine and pressed its usage at every opportunity. Yet, Freud's interest in cocaine eventually waned. Years later, Freud declared cocaine a "scourge" of humanity.

His first misgivings arose from a suffering friend, Dr. von Fleischl-Marxow, who suffered from severe pain caused by tumors along his peripheral nerves. Freud suggested that the anesthetic properties of cocaine might help, and soon Fleischl had escalated his daily dose to 1000 mg per day—approximately 20 times the amount Freud occasionally gave to himself. Eventually, Fleischl developed hallucinations, and on one occasion he saw "white snakes creeping over his skin." As the adverse effects of cocaine became known, cocaine use declined in Europe and North America (Freud, 1974; Jones, 1953).

Cocaine served as a key ingredient in Coca-Cola between 1886 and 1904 (**Figure 6.9**), along with another important ingredient, caffeine. The result of this combination, as displayed in the Coca-Cola advertisement in Figure 6.9, was a drink that reduced headache and relieved exhaustion. Although not a narcotic, which is defined as a sleep-inducing drug, the sale and distribution of "coca leaves, their salts, derivatives, or preparations" were regulated under the Harrison Narcotics Act of 1914. The act dealt primarily with the sale and distribution of opioids, which are narcotic drugs, but also listed cocaine among the drugs to be regulated. The association of cocaine with opioids led to cocaine's common designation as a narcotic, although this label doesn't accurately represent cocaine's pharmacological effects (Schultz, 1983). Cocaine remains classified as a narcotic by the U.S. Drug Enforcement Administration, despite other psychostimulant drugs, like methamphetamine, that do not have this designation.

**FIGURE 6.8** **Freud's *Über Coca***

Sigmund Freud provided some of the earliest characterizations of cocaine's pharmacological effects in *Über Coca*.



ÜBER COCA.

Von

DR. SIGM. FREUD

Secundararzt im k. k. Allgemeinen Krankenhause in Wien.

Neu durchgesehener und vermehrter Separat-Abdruck aus dem „Centralblatt für die gesammte Therapie".

WIEN. 1885.
VERLAG VON MORITZ PERLES

*Source:* Über Coca (Wien: 1885).

# STOP & CHECK

1. What are the primary psychoactive ingredients in ephedra?
2. The sale of ephedrine and pseudoephedrine is regulated in the United States and other countries because of the clandestine production of _____.
3. Why have bath salts become a concern for law enforcement agencies?
4. Which form of cocaine can be smoked? Why?

1. Ephedrine and pseudoephedrine 2. methamphetamine 3. Drugs sold as bath salts contain synthetic cathinone compounds that elicit psychostimulant effects. 4. The freebase form, which is referred to as crack cocaine. The boiling point for freebase cocaine allows it to be smoked in a pipe, whereas the vaporization point for the salt form of cocaine is too high to reach without special laboratory equipment.

**FIGURE 6.9 Advertisement for Coca-Cola**

Cocaine was a key ingredient in Coca-Cola between 1886 and 1904. The drink was advertised as a tonic that reduced headaches and relieved exhaustion.

Source: Copyright Coca-Cola 1897.

## Pharmacokinetics of Psychostimulants

### Routes and Forms of Psychostimulant Administration

The selected route of psychostimulant drug administration depends on the user's desired purpose for taking the drug. For achieving therapeutic effects, physicians prescribe psychostimulant drugs, such as amphetamine and methylphenidate, for oral administration in pill form. Methylphenidate is also available in liquid and skin patch form. For achieving rewarding effects, users prefer administration routes that provide rapid drug absorption, including intravenous injection, insufflation (or *snorting*), and inhalation.

The salt forms of psychostimulant drugs tend to allow for intravenous injections. To prepare amphetamine pills or methamphetamine crystals in salt form, the

substance is first ground into a fine powder. Then, it is mixed with a household chemical, which could be a chemical base or an organic solvent, to place the drug in a salt form. Because prescribed methylphenidate tablets contain the salt form of methylphenidate, recreational users crush the tablets in a fine powder. The synthetic cathinone drugs in bath salts already exist in salt form. Users dissolve the drug in salt form in water, making a drug solution that can be injected. Reports state that users administer synthetic cathinones through a wide variety of routes, including oral, insufflation (i.e., snorting), intravenous or intramuscular injection, and gingival (absorption through gums in mouth), among other routes (Prosser & Nelson, 2012).

The salt forms of these drugs also allow for insufflation. Users typically insufflate psychostimulant drugs by sharply inhaling lines of powder into a nostril through a short tube. This method places a substance into contact with membranes in the nose, throat, and lungs. The salt form is necessary for this route because drugs must be water soluble for proper absorption into these membranes.

The base forms of these drugs allow for inhalation. This is usually accomplished by heating the drug on a foil or plate or by heating the drug in a glass bulb or pipe. A *crack pipe* is a glass pipe used to smoke the freebase or crack form of cocaine. Smoking freebase cocaine can cause the release of **methylecgonidine**, a by-product of the freebase synthesis process that is harmful to the heart, lungs, and liver.

**Methylecgonidine**
By-product of the freebase synthesis process for cocaine that is harmful to the heart, lungs, and liver

Although intravenous injection, insufflation, and inhalation all provide quick absorption, the time courses among these routes vary. For example, Volkow and colleagues (2000) studied the peak drug effect onset times for a "high" for different routes of cocaine in cocaine-addicted individuals. Through the inhalation route, cocaine's peak subjective effects occurred after only 1.4 minutes. The intravenous route took twice as long to achieve peak effects, at 3.1 minutes, and insufflation produced the longest onset time for peak subjective effects, at 14.6 minutes (**Figure 6.10**). A drug's onset times can affect its addiction liability. Hatsukami and Fischman (1996), for example, found that cocaine addiction occurred more often for users who preferred inhalation and intravenous routes compared to users who preferred insufflation routes. Similarly, synthetic cathinone users report a quick "high" from insufflation or intravenous injection, compared to oral administration (Prosser & Nelson, 2012).

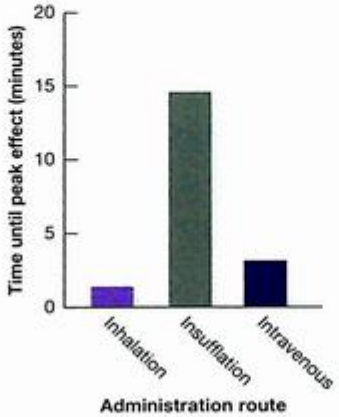
Other administration routes result in poorer absorption. Inhabitants of coca plant regions have long chewed coca leaves for their rejuvenating effects and for oral pain-relieving effects. Because the base form poorly penetrates mucous membranes, the leaves are often chewed with lime to improve water solubility. This in turn improves mucous-membrane absorption. Even with lime, only a small portion of cocaine absorbs through the mucous membranes. This isn't the case for all stimulants found in plants, however. Chewing khat leaves leads to 60 percent of cathinone absorption into mucous membranes (Toennes, Harder, Schramm, Niess, & Kauert, 2003).

## Biotransformation of Psychostimulants

Some psychostimulant drugs produce active metabolites in the liver, and many times these metabolites exhibit effects similar to the parent drug. For example, liver enzymes convert methamphetamine to amphetamine. By serving as a parent drug for amphetamine, methamphetamine administration produces psychostimulant effects from both methamphetamine and amphetamine.

**FIGURE 6.10 Cocaine Administration Routes and Peak Onset Times**

The time peak for research participants to feel a "high" from cocaine varies by administration route. Among these most common routes, inhalation provides a quicker onset time than either insufflation or intravenous injection.




*Source:* Adapted from Volkow et al. (2000).

We find active metabolites for cathinone and cocaine as well. Cathinone metabolism in the liver produces the active metabolite norephedrine, the *d* optical isomer of pseudoephedrine. Thus, cathinone administration leads to psychostimulant effects produced by itself *and* pseudoephedrine. Cocaine's active metabolite benzoylecgonine functions to constrict blood vessels as cocaine does (Madden, Konkol, Keller, & Alvarez, 1995).

Drug combinations may also interact to produce active metabolites. Combining cocaine with alcohol produces, through metabolism in the liver, the active metabolite cocaethylene, a compound with psychostimulant properties (Bradberry et al., 1993; McCance, Price, Kosten, & Jatlow, 1995; Rafla & Epstein, 1979). Through producing this psychostimulant, combined cocaine and alcohol use—an example of **polydrug use**—may provide greater rewarding effects than those produced by either drug alone (McCance et al., 1995). A similar reaction occurs after ingesting methylphenidate and alcohol, which results in the formation of the psychostimulant ethylphenidate. The production of such active metabolites suggests that polydrug use may increase the likelihood of abuse (Grant & Harford, 1990).

**Polydrug use**
The use of multiple substances, normally with the intention of achieving a specific effect

## Elimination of Psychostimulants

Amphetamine and methamphetamine have longer elimination rates than cocaine. The half-life for amphetamine is approximately 10 hours; similarly, the half-life of methamphetamine is approximately 11 hours. In comparison, cocaine's half-life is

approximately one hour, which accounts for shorter duration of psychostimulant effects than amphetamine and methamphetamine. Studies find a 1.5-hour half-life for cathinone, although we need pharmacokinetic information on the rapidly emerging synthetic cathinones (Toennes et al., 2003). Methylphenidate's half-life is approximately two hours, requiring additional administrations during a day for a steady drug effect. Given this, a physician may prescribe amphetamine (*Adderall*) for ADHD to school-age children in order to avoid having the medication wear off during a school day. Researchers are also developing new formulations of methylphenidate to prolong its effects (Childress, Sallee, & Berry, 2011).

## STOP & CHECK

1. Why might a user prefer to inhale psychostimulant drugs instead of resorting to other administration methods?
2. Why are knowing a drug's metabolites important for learning about psychostimulant effects?

1. The inhalation route offers quicker absorption than insufflation or even intravenous administration. 2. Many psychostimulant drugs alone or in combination with alcohol produce active metabolites, including those acting as psychostimulant drugs.

## Psychostimulants and Monoamine Neurotransmitters

### Amphetamines

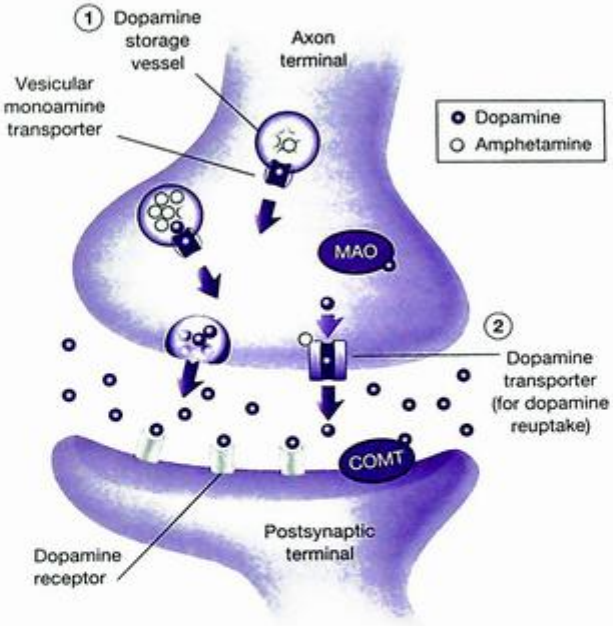
Amphetamines cause an increase in synaptic dopamine levels through two mechanisms of action (**Figure 6.11**). First, amphetamine expels dopamine from the neuron through dopamine membrane transporters. Amphetamine does this by causing a reversal in the direction of the dopamine transporter. Second, at high doses, amphetamine drugs prevent dopamine storage. Amphetamine and methamphetamine do this by entering dopamine storage vesicles through the vesicular transporter and displacing dopamine from the vesicle (Pifl, Drobny, Reither, Hornykiewicz, & Singer, 1995). Dopamine not stored in vesicles can be expelled into the cleft by membrane transporters—those with a reverse flow due to amphetamine—or will be broken down by enzymes.

**Review!** Dopamine enters vesicles through a vesicular transporter. After release, dopamine molecules re-enter the terminal through dopamine membrane transporters (Chapter 3).

**Review!** The enzyme MAO (monoamine oxidase) catabolizes (i.e., breaks down) dopamine and other monoamine neurons inside an axon terminal (Chapter 3).

**FIGURE 6.11 Effects of Amphetamines on Dopamine Neurotransmission**

Amphetamine and methamphetamine cause an increase in synaptic dopamine levels through (1) displacing dopamine from dopamine storage vesicles and (2) reversing the direction of the dopamine transporter. MAO enzymes can break down unstored dopamine in the axon terminal as well.




Amphetamine and methamphetamine also enhance serotonin and norepinephrine levels through acting at axonal terminals, but do so to a lesser extent than dopamine. Amphetamine and methamphetamine also prevent both serotonin and norepinephrine storage, and they reverse the direction of the membrane transporter for these neurotransmitters (Seidel et al., 2005).

## Methylphenidate and Cathinones

The pharmacological actions of methylphenidate resemble those of amphetamine. These drugs prevent reuptake of dopamine, serotonin, and norepinephrine but do

so with less efficacy than amphetamine. Also like amphetamine, methylphenidate prevents the storage of dopamine in synaptic vesicles (Pan et al., 1994).

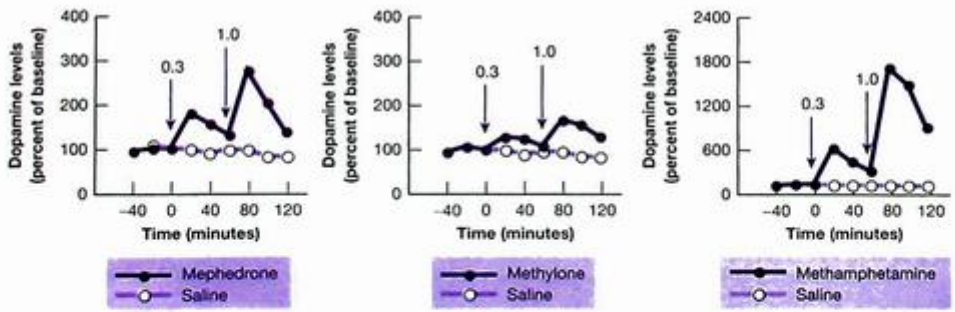
Given the dramatic increase in use of cathinone and synthetic cathinones, there has been an increased focus on evaluating the pharmacological actions of these drugs. Recent findings suggest that these drugs inhibit reuptake of dopamine, norepinephrine, and serotonin. Baumann and colleagues (2012) conducted radioligand binding experiments with two synthetic cathinones—mephedrone and methylone—to determine their binding affinity for dopamine, norepinephrine, and serotonin membrane transporters (see Box 4.1 for an overview of radioligand binding experiments). They next used microdialysis procedures to sample neurotransmitter levels in the nucleus accumbens of rats after administration of these drugs, in addition to testing methamphetamine for comparison. Both mephedrone and methylone increased levels of dopamine, although less so than levels produced by methamphetamine (**Figure 6.12**). Mephedrone and methylone also exhibited increased serotonin levels and were similar to serotonin levels produced by methamphetamine.

## Cocaine

The primary mechanisms of action for cocaine involve prevention of monoamine reuptake by blocking the membrane transporters for dopamine, norepinephrine, and serotonin (Chen, Sachpatzidis, & Rudnick, 1997; Jones, Garris, & Wightman,

**FIGURE 6.12** **Effects of Mephedrone, Methylone, and Methamphetamine on Nucleus Accumbens Dopamine Levels**

Mephedrone (left), methylone (center), and methamphetamine (right) increase dopamine concentrations in the nucleus accumbens. The *y*-axis refers to dopamine concentrations expressed as a percentage of predrug injection levels (i.e., baseline), and the *x*-axis represents the time course for the experimental session. The dose and injection times appear with arrows on the graph. The filled symbols represent the test drug, whereas empty circles represent a placebo condition (i.e., saline injections).

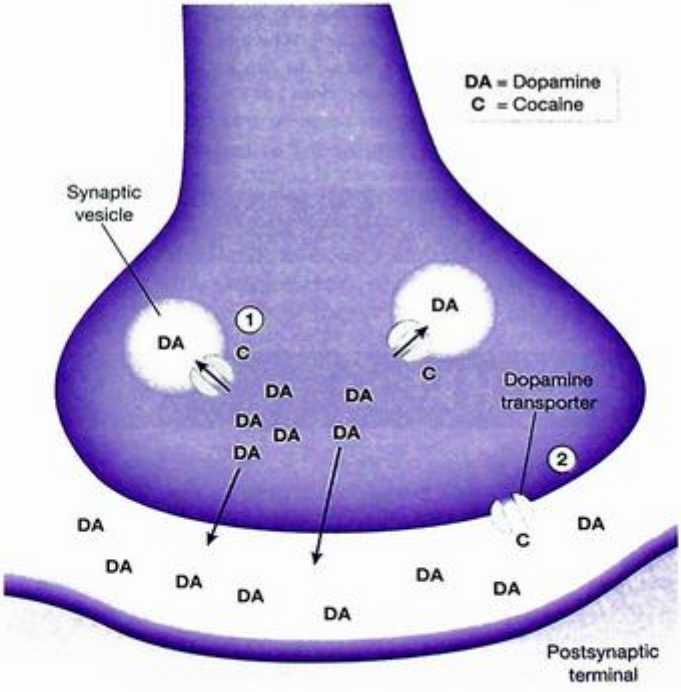



Source: Adapted from Baumann et al. (2012). "The Designer Methcathinone Analogs, Mephedrone and Methylone, Are Substrates for Monoamine Transporters in Brain Tissue." *Neuropsychopharmacology 37*, 1192–1203, Nature Publishing Group.

1995; Ritz, Cone, & Kuhar, 1990) (**Figure 6.13**). Further, cocaine *increases* transport of dopamine into synaptic vesicles, which may provide more stored dopamine for release (Brown, Hanson, & Fleckenstein, 2001). The active metabolite cocaethylene, produced after ingesting both cocaine and alcohol, also functions as a dopamine reuptake inhibitor (McCance et al., 1995). Within the brain reward circuitry, an enhanced concentration of dopamine in the nucleus accumbens by cocaine leads to the activation of dopamine receptors. The activation of $D_2$ receptors contributes to the rewarding effects of cocaine. Further, in animals trained to self-administer cocaine but then had responding extinguished, selective activation of $D_2$ receptors by a $D_2$ receptor agonist causes an immediate return to cocaine self-administration responding. That is, the effect produced by a $D_2$ receptor agonist appears as a reminder (or a "priming effect"), motivating drug-seeking behavior (Self, Barnhart,

**FIGURE 6.13 Effects of Cocaine on Dopamine Neurotransmission**

Cocaine enhances synaptic dopamine levels by 1) increasing dopamine transport into synaptic vesicles (providing more stored dopamine for release) and 2) reducing reuptake. Cocaine exhibits similar effects for norepinephrine and serotonin membrane transporters (not shown).



Lehman, & Nestler, 1996). The activation of dopamine $D_1$ receptors on GABA neurons in the nucleus accumbens accounts for associations of stimuli with cocaine's rewarding effects. In particular, GABA neurons expressing $D_1$ receptors appear most active when anticipating drug-associated stimuli (Calipari et al., 2016).

In high concentrations, cocaine acts as a $Na^{2+}$ channel blocker. This concentration far exceeds those necessary for producing the psychoactive effects just described, and actually will cause serious adverse effects and possibly death. However, these adverse effects can be avoided by applying cocaine locally; in doing so, cocaine serves as a local anesthetic. In fact, the discovery of these properties revolutionized ophthalmic surgery, because cocaine not only numbs the eye but also temporarily stops bleeding during surgery due to its vasoconstricting properties (i.e., constricts blood vessels) (dos Reis, 2009). These same vasoconstriction properties make cocaine still useful today as a treatment for stopping severe nose bleeds and as a local anesthetic for intranasal surgeries (e.g., Yung, Sharma, Jablenska, & Yung, 2015).

## Cocaine- and Amphetamine-Regulated Transcript

**Cocaine- and amphetamine-regulated transcript (CART)**
Peptide neurotransmitter produced after psychostimulant administration

The **cocaine- and amphetamine-regulated transcript (CART)** is a peptide neurotransmitter that is produced after psychostimulant administration. Acute administration of a psychostimulant drug causes the activation of the gene for CART, leading to the synthesis of the CART peptide, which is then stored in vesicles within axon terminals. CART peptides are found in the hypothalamus and mesolimbic dopamine system, where they increase dopamine release, although the precise mechanisms responsible for these actions remain unknown. CART peptides produce psychostimulant-like increases in locomotor activity. Yet, CART peptides also prevent psychostimulant-induced increases and dopamine-induced increases in locomotor activity (Jaworski, Kozel, Philpot, & Kuhar, 2003). Thus, CART alone produces psychostimulant-like effects, but CART in combination with a psychostimulant drug appears to counteract a psychostimulant's effects (Hubert, Jones, Moffett, Rogge, & Kuhar, 2008). In this way, CART might act to regulate the degree to which psychostimulant- and dopamine-induced effects can occur.

## STOP & CHECK

1. Through similar mechanisms, the amphetamines, methylphenidate, cathinones, and cocaine all enhance synaptic levels of the neurotransmitters _____, _____, and _____.
2. Unlike the other psychostimulants, what other actions does cocaine have?
3. What peptide neurotransmitter is released on acute administration of certain psychostimulant drugs?

1. dopamine, norepinephrine, serotonin (in any order) 2. At high doses, cocaine acts as a $Na^+$ channel blocker, which accounts for its local anesthetizing properties. 3. CART, which stands for cocaine- and amphetamine-regulated transcript.

# Pharmacological Effects of Psychostimulants

## Physiological Effects

Psychostimulant drugs produce most of their physiological effects by activating the sympathetic nervous system. Activation of the sympathetic nervous system increases heart rate, constricts blood vessels, relaxes airways, dilates pupils, inhibits salivation, inhibits digestion, and produces various other effects described in Chapter 2 (see **Table 6.3**). We find some suggestions of these effects in Sigmund Freud's *Über Coca*, mentioned previously in this chapter. Freud described a moderate increase in pulse rate that was "often accompanied by a rumbling . . . from high up in the intestine" (p. 58–59), an effect observed in two other individuals. These two individuals had also reported "an intense feeling of heat in the head" (p. 59), and Freud added, "I noticed this in myself" (Freud, 1974, p. 59).[2]

Activation of the sympathetic nervous system accounts for many of the uses and risks associated with psychostimulants. Psychostimulants ease nasal congestion by constricting swollen blood vessels in the sinuses and nasal passages. They also open airways in the lungs. These actions explain why ephedra is an effective herbal remedy for colds and why its main constituents, ephedrine and pseudoephedrine, serve as effective ingredients in cold medications.

Psychostimulants can cause hyperthermia, especially when used during strenuous physical exertion. Indeed, amphetamines contributed to the hyperthermia-related

**TABLE 6.3 Selected Objective and Subjective Psychostimulant Effects**

| Objective Effects | | |
|---|---|---|
| **Physiological Effects** | **Behavioral Effects** | **Subjective Effects** |
| Airway relaxation | Increased motor activity | Agitation |
| Blood vessel constriction (high blood pressure) | Psychosis, including hallucinations; formication with cocaine | Anxiousness |
| Dry mouth (reduced salivation) | | Euphoria |
| Increased heart rate | | Improved sense of well-being |
| Inhibited digestion | | Increased alertness |
| Increased body temperature | | Increased energy |
| Pupil dilation | | |
| Tooth decay with chronic use | | |

[2]This reference refers to an English translation of Freud's cocaine papers, including *Über Coca*. Freud's actual manuscript was published in 1885.

deaths of several athletes in the 1960s and 1970s (Wyndham, 1977). Wide public attention was given to ephedra after it contributed to the heat stroke-related death of Baltimore Orioles pitcher Steve Bechler in 2003.

**Anorectics**
Appetite-suppressant drugs

Psychostimulants also reduce appetite. As stated previously, psychostimulants served as appetite-suppressant drugs called **anorectics** during the 1950s and 1960s. In the 1990s, a combination therapy of the amphetamines fenfluramine and phentermine, together referred to as *fen-phen*, proved remarkably effective for weight loss. Another amphetamine, dexfenfluramine (*Redux*), was also used in combination with phentermine. Severe adverse cardiovascular effects resulting in heart valve damage and some deaths led to an abrupt decline of fen-phen treatments for obesity (Wadden et al., 1998).

Psychostimulants reduce hunger through actions in the hypothalamus, a key structure for the regulation of appetite. Within this structure, enhanced dopamine release contributes to appetite suppression. CART also plays a role in hunger. In the hypothalamus, CART is activated by the appetite-suppressing hormone leptin. Correlational studies suggest that impaired CART functioning, because of polymorphisms of the CART gene, is associated with obesity (Vicentic & Jones, 2007).

## Behavioral Effects

**Purposeful behavior (for psychostimulant use)**
Behavior that is goal directed; increased by lower doses of psychostimulants

**Rate-dependent effects**
Differing effects of a drug depending on the rate of behavior prior to drug administration

**Purposeless behavior (for psychostimulant use)**
Non-goal-directed behavior, may appear as habits; increased by higher doses of psychostimulants

**Stereotypy**
Psychostimulant-produced purposeless behavior

**Punding**
Psychostimulant-induced stereotypy in humans

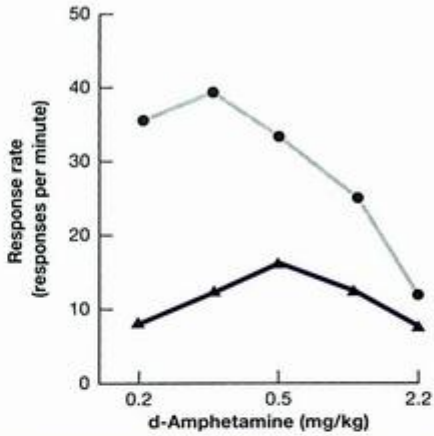
Increased behavioral activity is a key feature of psychostimulant drugs. These effects are dose dependent and affect both purposeful and purposeless behavior. At lower doses, psychostimulants produce an increase in **purposeful behavior**—that is, it appears to be goal directed. For example, a laboratory rat pressing a lever to receive food reinforcers is engaging in purposeful behavior. Relatively low doses of psychostimulants can cause *faster* lever pressing. In humans, an increase in purposeful behavior may result in fast speech or faster completion of various tasks. Increased purposeful behavior occurs from increased dopamine concentrations in the nucleus accumbens (Ellinwood, King, & Lee, 2000).

These activity changes in purposeful behavior also have rate-dependent effects. For drugs, **rate-dependent effects** reflect differences in a drug's behavioral effects as a function of predrug administration response rates (Ginsburg, Pinkston, & Lamb, 2011). Psychostimulant drugs increase low rates of baseline behavioral activity. At the same time, psychostimulant drugs decrease high rates of baseline behavioral activity. As shown in **Figure 6.14**, for example, amphetamine increased activity in rats that had relatively low rates of lever pressing. However, amphetamine *decreased* activity in rats that had a relatively high rate of lever pressing (MacPhail & Gollub, 1975).

At higher doses, psychostimulants produce an increase in **purposeless behavior**, which occurs as non-goal-directed behavior that appears habitual. In nonhuman animals, this increase in purposeless behavior is called **stereotypy**. Stereotypy in rodents is characterized by repetitive grooming, head swaying, gnawing, or licking. In humans, we refer to stereotypic effects as **punding**. Punding may consist of repetitive teeth grinding, tapping, skin picking, or nail biting. Increased dopamine concentrations in dorsal portions of the basal ganglia, particularly the caudate nucleus, appear most associated with purposeless behavior (Ellinwood et al., 2000).

**FIGURE 6.11 Rate-Dependent Effect of Psychostimulant Drugs**

D-amphetamine reduces high response rates (circles) and increases low response rates (triangles) at an appropriate dose—0.5 mg/kg—in rats.




Source: Adapted from data from MacPhail and Gollub (1975)

## Subjective Effects

In humans, low doses of psychostimulants provide feelings of increased energy, alertness, a sense of well-being, enthusiasm, and other positive emotional effects (Smith & Davis, 1977). Such doses are used to combat fatigue and reduce the symptoms of narcolepsy. Higher doses of psychostimulants, when administered through a route that offers rapid absorption, produce a "rush" and euphoria. Active metabolites that function as psychostimulants enhance these effects.

**Review!** Subjective effects are uniquely experienced by the individual and cannot be directly observed by others. Objective effects can be measured by recording overt behavior or physiological events (Chapter 1).

Drug discrimination procedures measure the subjective effects of psychostimulants (**see Box 6.1**). For example, Johanson, Lundahl, Lockhart, and Schubiner (2006) used a drug discrimination procedure to determine whether human participants experience the same subjective effects for cocaine as they do for methamphetamine. During training, the participants were rewarded with money for correctly identifying a cocaine-like effect or non-cocaine-like effect. After learning to accurately discriminate between these two conditions, the participants were administered methamphetamine instead of cocaine. Most of the participants indicated that they had received cocaine in this procedure. We infer from these results that the subjective effects of cocaine and methamphetamine are similar.

# BOX 6.1

## DRUG DISCRIMINATION

A *drug discrimination procedure* trains an organism to recognize or discriminate between the subjective effects of a particular drug compared to noticeably different effects. This procedure is used in other animals and humans to assess the subjective effects of both recreational and therapeutic drugs.

Drug discrimination procedures often are conducted in rats, pigeons, or monkeys using operant chambers. In a typical design, researchers select a *training drug*, which is a psychoactive of interest for the study. The training drug is also called a *discriminative stimulus*, because it signals an opportunity for reinforcement. After administration of the training drug, the animal is placed into the operant chamber containing two levers: buttons (often referred to as *keys*) or some other type of operandi. Only responses on one operandum will be reinforced, usually by delivery of a food pellet or small water cup. On a different day, the organism is administered the training drug vehicle, the inert solution in which the drug was dissolved, and only responses on the other operandum will be reinforced. After extensive training, an organism learns to associate one operandum with the training drug's subjective effects and the other operandum with the absence of the training drug's effects (Porter, Prus, & Overton, 2018).

Note that *drug discrimination* and *self-administration* procedures are different. In a self-administration procedure, which is used for break point studies, animals produce a behavioral response to *receive a drug injection*. In a drug discrimination procedure, animals must attend to a drug's subjective effects in order to receive food, water, or other type of reinforcer.

To place the drug discrimination procedure into context, consider the following study by de la Garza and Johanson (1985) using pigeons. The operandi used in this study were two response keys (basically pressable buttons on the chamber wall). One key was associated with cocaine and the other was associated with *saline*—that is, the absence of cocaine's stimulus effects. These cocaine or saline training conditions alternated in daily sessions until the pigeons correctly responded to each condition with greater than 90-percent accuracy.

After training, the pigeons were administered different drugs to determine whether the pigeons responded on the cocaine key, indicating cocaine-like stimulus effects, or the saline key, indicating *non*-cocaine-like stimulus effects. **Box 6.1 Figure 1** shows these study results.

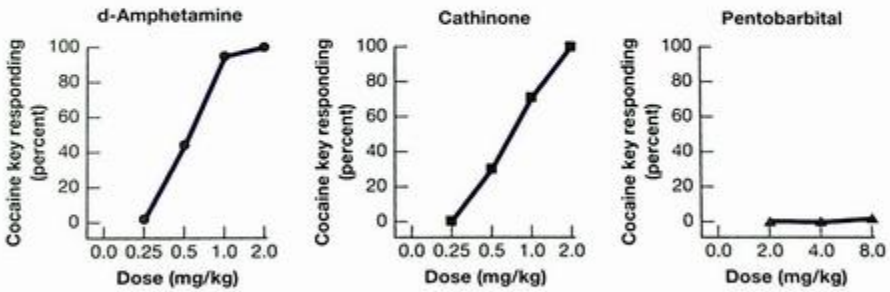
These figures show the percentage of pecking that occurred on the cocaine key during test sessions for each drug and dose tested. At 1.0 mg/kg and 2.0 mg/kg doses, d-amphetamine caused almost all of the key pecks to occur on the cocaine key. Similarly, the highest dose of cathinone produced nearly all pecks on the cocaine key. Both d-amphetamine and cathinone are psychostimulant drugs that have similar subjective effects as cocaine and may represent the stimulus effects of cocaine in this task. However, pentobarbital, a barbiturate that exhibits very different subjective effects than cocaine, resulted in few pecks on the cocaine key.

Human drug discrimination procedures are similar to animal drug discrimination procedures. In place of an operant chamber, human participants emit responses on a computer mouse; clicks usually substitute for key pecks or lever presses. Money usually serves in place of food pellets.

There are many variations on the typical drug discrimination design. For example, two or more training drugs may be used in the same procedure, or there may be more than two operandi used in an operant chamber. These design variations can provide a further resolution of the biological actions supporting a drug's subjective effects.

**BOX 6.1 FIGURE 1** **Psychostimulant Effects in a Drug Discrimination Procedure**

The psychostimulant drugs d-amphetamine (left) and cathinone (middle), but not the barbiturate pentobarbital (right), engendered cocaine key responding in a cocaine drug discrimination task in pigeons. These findings suggest that d-amphetamine and cathinone produce subjective effects similar to those of cocaine. The *y*-axis refers to the percentage of key pecks occurring on the cocaine key, and the *x*-axis refers to the dose of the drug.




Source: Data from de la Garza and Johanson (1985).

As presented in Chapter 5 (Box 5.1), break points also assess the strength of positive mood effects of psychostimulant drugs. For example, **Figure 6.15** shows the results of break point studies conducted in rats using d-amphetamine, methamphetamine, cocaine, and other psychostimulants. In these studies, the break points for the highest doses of d-amphetamine and methamphetamine are both found at 268 responses per reinforcer. The break point for cocaine was 178 responses, lower than either d-amphetamine or methamphetamine. Thus, the rats worked harder to receive d-amphetamine and methamphetamine than they did to receive cocaine (Richardson & Roberts, 1996).

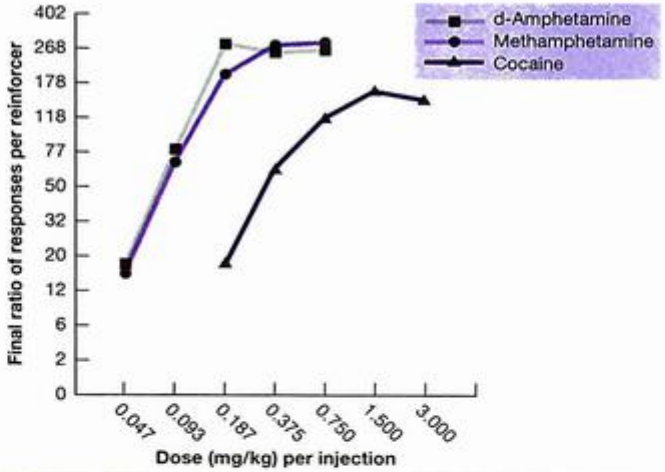
**Review!** A break point is the maximum level of responding a subject is willing to do in order to receive a drug injection (Chapter 5).

## Adverse Effects

Psychostimulants produce many adverse physiological effects. Among the most prominent are cardiovascular dysfunction, pulmonary dysfunction, abnormal fetal development, and tooth decay. Adverse effects also occur from the conditions of drug use. Drug administration in unclean environments or through shared needles exposes users to a high risk of infection. Among the most common diseases associated with abuse of intravenously administered drugs are human immunodeficiency virus (HIV), hepatitis, and tuberculosis (Brecher, 1972; Cadet & Krasnova, 2007; Ellinwood et al., 2000).

**FIGURE 6.15 Self-Administration for Selected Psychostimulant Drugs**

The break point for three psychostimulant drugs is shown as the highest "final ratio" completed. On the bottom (*x*-axis) is the amount of drug delivered per injection. Cocaine, shown by the triangles, had a lower break point than both d-amphetamine (squares) and methamphetamine (circles).




*Source:* Adapted from Richardson & Roberts (1996).

Cardiovascular effects represent the greatest risk of psychostimulant use. Enhanced sympathetic nervous system activation taxes the cardiovascular system by constricting blood vessels and increasing heart rate. These actions lead to an increased risk of hypertension, stroke, aortic rupture, and heart attack. Hypertension during psychostimulant use is an important cause of abnormal fetal development. Through blood vessel constriction, total blood flow to the fetus is reduced, causing limited oxygen availability and nutrient delivery. These effects, in turn, contribute to lower fetal growth and the risk of severe injury to the fetus, including hemorrhage, ischemia, and neuronal death.

The adverse effects on pulmonary function include injury during inhalation, hemorrhaging, edema, and tissue inflammation. Normal pulmonary function is compromised when sympathetic nervous system activity is significantly enhanced as well as when the lungs are exposed to vapor from inhaled methamphetamine or crack cocaine. Smoking these drugs exposes the lungs to the drug as well as any harmful by-products produced during the drug's synthesis (Ellinwood et al., 2000; Lineberry & Bostwick, 2006).

**Meth mouth**
Tooth decay caused by methamphetamine use

Among the psychostimulant drugs, methamphetamine use is most associated with tooth decay, a condition referred to as "**meth mouth.**" The American Dental Association describes these teeth as "blackened, stained, rotting, crumbling, or falling apart" (American Dental Association, 2005, p. 1491). Meth mouth occurs even when methamphetamine does not contact the teeth.

Important contributing factors for meth mouth include poor dental hygiene, such as brushing and flossing, as well as damaged gums due to contact with inhaled chemicals during drug use. Two other contributing factors for meth mouth occur from activation of the sympathetic nervous system. First, methamphetamine's activation of the sympathetic nervous system reduces salivation, which has important protective properties for preventing tooth decay. Second, reduced saliva causes *dry mouth*, which motivates a methamphetamine user to drink fluids. Methamphetamine users tend to consume sugary soft drinks, and exposing teeth to sugar, particularly in the absence of saliva's tooth-protective properties, leads to cavities and tooth decay (Klasser & Epstein, 2005).

Psychostimulants also produce psychosis at high doses. **Psychostimulant-induced psychosis** is similar to symptoms of schizophrenia, including paranoia, agitation, and auditory hallucinations. Given that psychostimulants enhance brain dopamine levels, psychostimulant-induced psychosis suggests that abnormally high dopamine levels exist in schizophrenia. Yet, psychostimulant-induced psychosis differs from psychosis in schizophrenia. First, many psychostimulant hallucinations are tactile. High psychostimulant doses cause **formication**, a tactile hallucination described as feeling like insects or worms crawling under the skin. Such tactile hallucinations are less common for schizophrenia. Second, psychostimulant-induced psychosis often includes visual hallucinations and occasional olfactory hallucinations. Psychosis in schizophrenia mainly consists of auditory hallucinations.

**Psychostimulant-induced psychosis**
Psychotic behavior caused by psychostimulant use

**Formication**
A tactile hallucination described as feeling like insects or worms crawling under the skin

## STOP & CHECK

1. Activation of the _____ nervous system accounts for many of the physiological objective effects of psychostimulant drugs.
2. Appetite-suppressant effects are the reason why psychostimulant drugs have been used to treat _____.
3. Although low psychostimulant doses may increase purposeful behavior, high psychostimulant doses may increase _____ behavior.
4. How do subjective effects of cocaine compare to methamphetamine?

1. sympathetic 2. obesity 3. purposeless 4. Both drugs produce euphoria and other positive mood effects. Moreover, humans trained to recognize the subjective effects of cocaine misidentify methamphetamine as cocaine.

## Psychostimulant Drugs Produce Sensitization and Tolerance

Either sensitization or tolerance can occur from repeated use of psychostimulants. Sensitization tends to occur for *purposeless* behavior. In rats, sensitization presents as an increase in stereotypic behaviors such as sniffing and head movements

(Robinson & Becker, 1986). Repeated administration of psychostimulant drugs may also lead to incentive sensitization, which may play an important role in the development of psychostimulant addiction (Robinson & Berridge, 2003).

**Review!** Incentive salience describes the heightened neurobiological and behavioral responses to stimuli associated with drug use (Chapter 5).

Tolerance occurs to the positive subjective effects of psychostimulants by creating a need to use higher doses of a psychostimulant drug to achieve these effects. However, the initial "high" first felt from a psychostimulant drug can be hard to achieve. Cocaine users, for example, seldom experience the same rush they felt on first using cocaine, and efforts to achieve this same intense rush are a driving force in cocaine addiction.

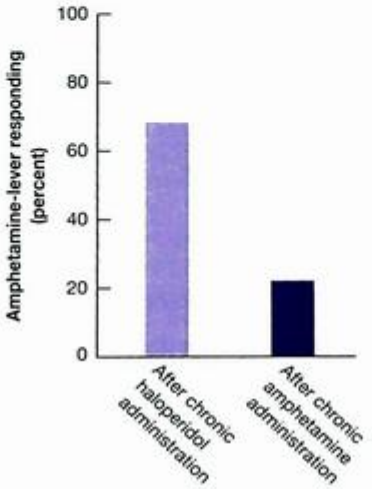
We find that a key form of psychostimulant tolerance is *pharmacodynamic tolerance*. Although many pharmacological actions may play a role, pharmacodynamic tolerance relies in part on changes in dopamine $D_2$ receptor sensitivity. Barrett, White, and Caul (1992) demonstrated a link between $D_2$ receptors and repeated psychostimulant administration using a drug discrimination procedure. In this study, rats learned to discriminate the $D_2$ receptor antagonist haloperidol[3] versus the psychostimulant drug d-amphetamine. The latter causes $D_2$ receptor activation by enhancing synaptic dopamine levels. After learning this discrimination, a chronic treatment regimen was employed. During this regimen, animals were treated either with haloperidol or with d-amphetamine for 10 consecutive days. On the day after treatment ended, the rats were placed in the operant chamber without a drug injection and were free to choose the appropriate lever, either haloperidol or amphetamine. Rats chronically treated with haloperidol chose the amphetamine lever, whereas rats chronically treated with d-amphetamine chose the haloperidol lever (**Figure 6.16**). This happened because pharmacodynamic tolerance developed over the course of the treatment regimen. The study authors speculated that synaptic sites adapted to haloperidol's repeated blockade of $D_2$ receptors by increasing the sensitivity of $D_2$ receptors. Similarly, the synaptic sites adapted to repeated activation of $D_2$ receptors by d-amphetamine by decreasing the sensitivity of $D_2$ receptors. When they returned the rats to the operant chamber for a drug discrimination test, chronically treated haloperidol rats had an oversensitive dopamine state; these effects resembled d-amphetamine-like stimulus effects. Similarly, the chronically treated d-amphetamine rats had an under-sensitive dopamine state; these effects resembled haloperidol-like stimulus effects.

*Cross tolerance* also occurs between psychostimulant drugs. In an early characterization of psychostimulant cross tolerance, Woolverton, Kandel, and Schuster (1978) demonstrated that rats tolerant to cocaine-induced reductions in milk intake exhibit this same tolerance when treated with amphetamine. The same was true when amphetamine-tolerant rats were treated with cocaine.

[3] also a typical antipsychotic drug

**FIGURE 6.16** **Demonstration of Sensitization and Tolerance Using a Drug Discrimination Procedure**

In rats trained to discriminate haloperidol versus amphetamine in a two-lever drug discrimination task, a test session conducted after chronic administration of haloperidol (left) led to increased amphetamine-lever responding, whereas a test session conducted after chronic administration of amphetamine (right) led to decreased amphetamine-lever responding (see text for further details). The *y*-axis refers to percent of responses occurring on the amphetamine lever.




*Source:* Data from Barrett et al. (1992).

A psychostimulant drug's dosing frequency—intermittent or continuous—plays an important role in determining whether sensitization or tolerance will occur. Sensitization occurs after a period of intermittent dosing of psychostimulants, whereas tolerance occurs after continuous dosing of psychostimulants. Generally, intermittent dosing consists of using a drug after all of the drug, as well as similarly acting metabolites, from past use has been eliminated from the body. Given the half-life of amphetamine in humans, two or three amphetamine administrations per week might qualify as intermittent drug administration. Continuous dosing consists of a user administering a drug while drug molecules (or similarly acting metabolites) from a previous administration remain in the body. Depending on the particular drug, continuous administration might consist of one or multiple administrations per day (Ellinwood et al., 2000).

## STOP & CHECK

1. In addition to sensitization for purposeless behavior, what other type of sensitization occurs during long-term use of psychostimulant drugs?
2. Reduced $D_2$ receptor sensitivity after prolonged administration of a psychostimulant drug is an important mechanism of _____ tolerance.
3. Cross tolerance implies that an individual who tolerates high doses of cocaine would tolerate _____ doses of amphetamine.

1. In addition to sensitization to purposeless behavior, incentive sensitization may also occur. 2. pharmacodynamic 3. high

## Psychostimulant Addiction

### *Linking Pharmacological Actions to Reinforcing Effects*

Increased dopamine neurotransmission in the nucleus accumbens mostly accounts for the reinforcing effects of psychostimulant drugs. In particular, these actions rely on dopamine $D_2$ receptors. The positive subjective effects of d-amphetamine, for example, can be blocked by $D_2$ receptor antagonists such as the antipsychotic drug haloperidol.

For cocaine, reinforcing effects also depend on the activation of dopamine $D_1$ receptors and serotonin neurotransmission. Greater activation of $D_1$ receptors occurs because of cocaine-induced elevations in dopamine levels. Caine and colleagues (2007) demonstrated the importance of $D_1$ receptors using self-administration procedures in dopamine $D_1$ receptor knock-out mice and wild-type mice. The wild-type mice readily learned to self-administer cocaine in this procedure, but none of the $D_1$ receptor knock-out mice learned to self-administer cocaine. Serotonin transporter blockade also contributes to cocaine's subjective effects. For example, serotonin transporter knock-out rats exhibit enhanced cocaine self-administration, hyperactivity, and conditioned place preference compared to wild-type rats (Homberg et al., 2008).

**Review!** Receptor knock-out mice lack certain receptors as a result of genetic modification. Wild-type mice are not genetically modified (Chapter 2).

The withdrawal symptoms associated with psychostimulants primarily occur as psychological effects rather than physiological effects. Just as psychostimulants produce increases in activity, enjoyment, and euphoria, withdrawal from psychostimulants produces lethargy, lack of joy, and *dysphoria*, which is characterized as feelings of hopelessness, unhappiness, and discomfort.

### *Genetics Influence the Susceptibility to Psychostimulant Addiction*

Genetic animal studies provide a framework for identifying possible links between human genetic differences and susceptibility to psychostimulant addiction. There are three primary ways that genetic differences alter psychostimulant drug effects.

First, genetic differences can alter the rate of drug metabolism. If an individual's genetic expression of P450 enzymes leads to a quicker metabolism of a psychostimulant drug, this will shorten the duration of the drug's effects. Shorter drug effects may lead to more frequent drug use. Second, a genetic predisposition can enhance the subjective effects of psychostimulant drugs. Individuals have a greater risk of drug addiction if they experience powerful reinforcing effects. Third, a genetic predisposition can alter the negative effects of psychostimulant drugs. Drug addiction is unlikely to develop for an individual who experiences adverse effects or negative subjective effects after acute use (Haile, Kosten, & Kosten, 2009).

The **C-1021T polymorphism** has received much attention by psychostimulant addiction researchers. This polymorphism causes low expression of dopamine β-hydroxylase, the enzyme that converts dopamine to norepinephrine. Based on animal research that evaluated inhibitors of dopamine β-hydroxylase, psychostimulants likely exhibit lower norepinephrine release for those with lower dopamine β-hydroxylase expression compared to those exhibiting normal dopamine β-hydroxylase expression (Schroeder et al., 2010).

**C-1021T polymorphism** Polymorphism that causes low expression of dopamine β-hydroxylase, the enzyme that converts dopamine to norepinephrine

Through these actions, the C-1021T polymorphism may increase the negative subjective effects of psychostimulants. Kalayasiri and colleagues (2007) studied the relationship between the C-1021T polymorphism and cocaine's subjective effects. This study used a cocaine self-administration experiment in humans with the C-1021T polymorphism. A greater degree of paranoia was observed in participants homozygous for the C-1021T polymorphism compared to other study participants. Cocaine users consider paranoia an aversive effect; some individuals experience and report paranoia and other features of psychosis and cite these as reasons for seeking addiction treatment (Brady, Lydiard, Malcolm, & Ballenger, 1991).

### *Sex Differences in Psychostimulant Addiction*

For all illicit substances, including psychostimulants, we find rates of use higher for men than women (Center for Behavioral Health Statistics and Quality, 2014a). However, a number of findings suggest that women are particularly at risk for developing a psychostimulant addiction. Compared to men, women start using cocaine at an earlier age (Griffin, Weiss, & Lange, 1989). Women are also more likely to engage in binge cocaine use, use cocaine more frequently, and matriculate from first cocaine use to dependent use at a faster rate (Chen & Kandel, 2002; McCance-Katz, Carroll, & Rounsaville, 1999).

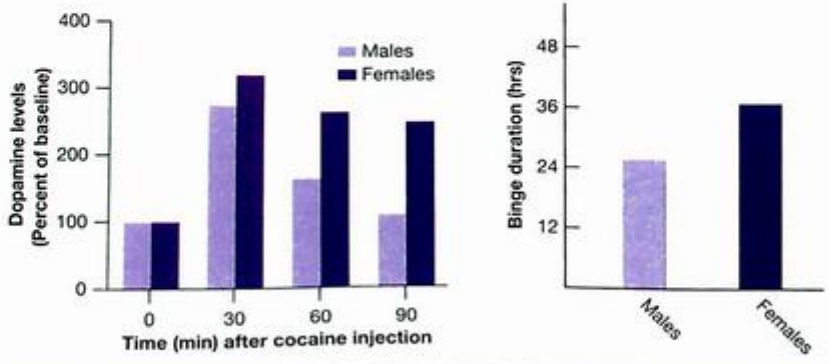
The potential reasons for a greater risk of cocaine addiction in women include estradiol and progesterone levels and susceptibility to stress (Becker & Hu, 2008). During the follicular phase of the menstrual cycle, when estradiol slowly rises from low levels during the phase and progesterone levels are low, women

report enhanced positive subjective effects from d-amphetamine use compared to use during the luteal phase, characterized by moderate estradiol and high progesterone levels. In female rats, administration of estrogen enhances the dopamine release produced by cocaine and appears necessary for CART-induced dopamine turnover in the nucleus accumbens (Shieh & Yang, 2008; Tobiansky et al., 2016). Studies also suggest that progesterone may weaken the subjective effects of psychostimulants (Becker & Hu, 2008).

Women who become psychostimulant dependent may have stronger reactions to stressors. For example, Back, Brady, Jackson, Salstrom, and Zinzow (2005) found that cocaine-dependent women reported greater feelings of stress than cocaine-dependent men after completing stressful tasks in a laboratory setting. Sinha and colleagues (2007) found that cocaine-dependent women studied during the luteal phase reported feeling lower stress and less craving for cocaine than cocaine-dependent women studied during the follicular phase. Stress may also affect dopamine levels and pattern of drug administration in males versus females, based on studies in rats. Holly, Shimamoto, DeBold, and Miczek (2012) applied stressors to male and female rats, finding that stressed females (a) exhibited a greater duration of enhanced dopamine levels in the nucleus accumbens, and (b) engaged in a greater overall duration of "binge" (a period of frequent self-administration) cocaine self-administration episodes compared to stressed males when given free access to cocaine over a 48-hour period (**Figure 6.17**).

**FIGURE 6.17** **Sex Differences and Cocaine Self-Administration**

Cocaine administration causes stressed female rats to exhibit a longer duration of elevated dopamine levels in the nucleus accumbens compared to stressed male rats (left). The *y*-axis shows the percentage of dopamine levels compared to pre-cocaine administration. The *x*-axis shows time points when the samples were taken. Stressed female rats also exhibit a greater duration of cocaine self-administration binges compared to stressed male rats (right).




Source: Adapted from Holly, Shimamoto, DeBold, and Miczek (2012).

## STOP & CHECK

1. Which dopamine receptors are important for the reinforcing effects of psychostimulant drugs like cocaine and amphetamine?
2. How might the C-1021T polymorphism affect norepinephrine levels after cocaine use?
3. What role might estradiol play in the subjective effects of psychostimulants?

1. Dopamine $D_2$ and $D_3$ receptors 2. Given that people with the C-1021T polymorphism have a poorer ability to synthesize norepinephrine from dopamine, that may lead to lower norepinephrine levels. 3. Estradiol increases cocaine-induced elevations in nucleus accumbens dopamine release, which might be expected to enhance the positive subjective effects of cocaine.

### Treatments for Psychostimulant Addiction

The therapies for psychostimulant addiction address two primary phases of recovery: abstinence and relapse. Abstinence begins with detoxification from a drug and then consists of a state of no drug use. During detoxification (*detox*), the withdrawal effects of psychostimulant use are most prominent. Treatment for detoxification typically involves hospitalization and medical treatment.

One treatment is *disulfiram*, a medication used to treat alcohol addiction (**Table 6.4**). Disulfiram is an inhibitor of dopamine β-hydroxylase, an enzyme that converts dopamine to norepinephrine. In norepinephrine neurons, disulfiram causes reduced production of norepinephrine. We learn more about disulfiram in Chapter 8 on alcohol since disulfiram interferes with alcohol metabolism. In clinical studies, disulfiram reduces cocaine's positive subjective effects, including a reduced high or rush, and enhanced negative subjective effects, including paranoia, agitation, and nervousness (Baker, Jatlow, & McCance-Katz, 2007; Hameedi et al., 1995). Individuals with a C-1021T polymorphism—who already have a lower expression of dopamine β-hydroxylase—are even more susceptible to negative subjective effects from disulfiram and cocaine administration (Haile et al., 2009). However, the ability of disulfiram to reduce positive subjective effects may depend on dosage. For example, Oliveto and colleagues (2011) found that lower doses of disulfiram increased the frequency of cocaine use over several weeks of treatment in cocaine-addicted users.

Many studies have evaluated *modafinil (Provigil)* for aiding psychostimulant detoxification. Modafinil engenders mild psychostimulant effects and has approved therapeutic uses for narcolepsy. Like other psychostimulants, modafinil elevates dopamine levels in the nucleus accumbens, yet these elevations are lower and longer lasting compared to other psychostimulant drugs (Zolkowska et al., 2009). Modafinil also increases glutamate levels in the nucleus accumbens after chronic cocaine use (Mahler et al., 2014). These actions may make modafinil a safe substitute for abused psychostimulant drugs.

**Review!** Rewarding effects can be produced by activating glutamate receptors in the nucleus accumbens (Chapter 5).

**TABLE 6.4 Drugs Used for Psychostimulant Addiction**

| Name of Drug(s) | Mechanism of Action | Uses |
|---|---|---|
| Disulfiram (brand names: *Antabuse* or *Antabus*) | Inhibits aldehyde dehydrogenase and dopamine β-hydroxylase | Treatment of cocaine addiction by diminishing positive subjective effects and enhancing negative subjective effects; also treatment for alcohol addiction |
| Modafinil (brand name: *Provigil*) | Elevates dopamine levels in the nucleus accumbens | Substitute for psychostimulant effects to diminish withdrawal; may prevent relapse |
| Imipramine (brand name: *Tofranil*); other tricyclic antidepressant drugs | Elevates dopamine, norepinephrine, and serotonin levels | Diminishes withdrawal effects by compensating for underactive monoamine neurotransmission during withdrawal |
| Topiramate (brand name: *Topamax*); other drugs: vigabatrin (*Sabril*) | Facilitates GABA neurotransmission; otherwise, used to treat seizures | Prevents relapse by interrupting associative learning processes for preoccupation and anticipation stage of addiction |

To investigate modafinil as a treatment for psychostimulant addiction, Dackis, Kampman, Lynch, Pettinati, and O'Brien (2004) evaluated eight weeks of modafinil treatment, combined with psychotherapy, in cocaine-addicted individuals enrolled in an outpatient treatment program. Researchers collected and tested urine samples each week to determine abstinence from cocaine. During the course of the study, modafinil significantly increased the number of patients remaining abstinent from cocaine. Although these study results show promise, another study using modafinil failed to show changes in the frequency of cocaine use in addicted users (Anderson et al., 2009).

Tricyclic antidepressant drugs such as imipramine effectively reduce craving, depression, and other withdrawal symptoms during psychostimulant detoxification. Chronic tricyclic antidepressant treatment elevates dopamine, norepinephrine, and serotonin levels, which may address a deficiency in these neurotransmitters during psychostimulant withdrawal. Addressing these deficiencies can aid in relapse prevention. For example, in an assessment of methamphetamine relapse rates, imipramine treatment was associated with significantly longer stays in a free drug addiction clinic (Galloway, Newmeyer, Knapp, Stalcup, & Smith, 1996).

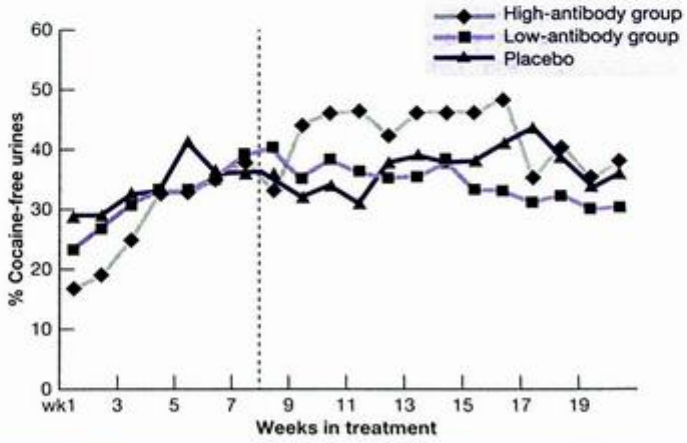
Drugs that facilitate GABA neurotransmission also demonstrate clinical efficacy for preventing psychostimulant relapse. For example, the anticonvulsant drug topiramate (*Topamax*) is commonly used for cocaine relapse prevention. In one clinical study, 60 percent of former cocaine-dependent patients treated with topiramate were completely abstinent for more than three weeks, compared to 26 percent of those

treated with placebo (Kampman et al., 2004). Another anticonvulsant drug, vigabatrin (*Sabril*), provided similar improvements in treatment outcomes for cocaine-addicted patients (Kampman, 2010). Drugs that facilitate GABA neurotransmission may interrupt associative learning processes important during the preoccupation and anticipation stage of addiction. By interrupting these processes, these treatments may weaken sensitized incentive processes for drug seeking and use (Koob & Volkow, 2009).

Finally, an experimental approach consists of vaccinating against psychostimulant effects as a way to prevent or eliminate abuse (Shen, Orson, & Kosten, 2012). A vaccine would produce antibodies that bind to a psychostimulant drug and prevent the drug from crossing the blood–brain barrier or otherwise make the substance inert. Kosten and colleagues (2014) have evaluated a potential cocaine vaccine in cocaine-dependent users. In one of these studies, the researchers found more cocaine-free urine samples for those with high antibody levels compared to those with low antibody levels or placebo. These results were evident after eight weeks, the amount of time needed for antibodies to reach sufficient levels (**Figure 6.18**). Yet even in the high-antibody group, researchers found that less than 50 percent of

**FIGURE 6.18** **Effects of a Cocaine Vaccine on Cocaine Use**

No differences were shown between the groups during the first eight weeks after injection of the vaccine, which was the time necessary for sufficient antibody levels to develop. Some participants produced high levels of antibodies (labeled the "High-antibody group"), and some produced low levels of antibodies (labeled the "Low-antibody group"). The *y*-axis shows the percentage of users testing negative for cocaine in the body; the *x*-axis shows each week following injection of the vaccine. The dashed vertical line shows the time point (eight weeks) at which enough antibodies should have been sufficiently produced to act on cocaine molecules.




*Source:* Adapted from Martell et al. (2009).

patients were ultimately cocaine free; further, fewer cocaine-abstinent users were found a few weeks later (Martell et al., 2009). A later study from the group reported similar results (Kosten et al., 2014). Thus, although this approach may have appeal, further vaccine development is needed.

## STOP & CHECK

1. What are the two primary aims of pharmacological treatment for psychostimulant addiction?
2. For the treatment of psychostimulant addiction, how might disulfiram drug therapy be related to the C-1021T polymorphism?
3. What are the shared pharmacological mechanisms for modafinil and tricyclic antidepressants that may be important for treating psychostimulant addiction?

1. To treat withdrawal symptoms during abstinence and prevent relapse. 2. Like individuals with the C-1021T polymorphism, disulfiram lowers the expression of dopamine β-hydroxylase, causing unpleasant subjective effects to occur when a psychostimulant is administered. 3. Modafinil and tricyclic antidepressants increase dopamine, norepinephrine, and serotonin concentrations just as amphetamine and cocaine do. In this way, these drugs may provide a replacement of these elevated neurotransmitters during psychostimulant use.

## From Actions to Effects: Psychostimulants as Cognitive Enhancers and Treatments for ADHD

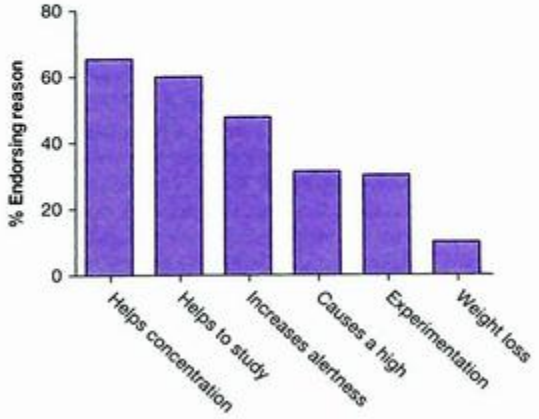
**Cognitive-enhancing drugs (or smart drugs or nootropics)**
Improve concentration, memory, or other cognitive functions

Aside from their potential as addictive substances, we find instrument use of psychostimulants for the purpose of enhancing cognitive functioning. **Cognitive-enhancing drugs** (or **smart drugs** or **nootropics**) improve concentration, memory, or other cognitive functions. Compounds generally used as cognitive enhancers consist of modafinil or treatments for ADHD, such as methylphenidate (*Ritalin*), amphetamine (in the form of *Adderall*), or lisdexamfetamine dimesylate (*Vyvanse*). This differs from so-called "*soft cognitive enhancers*," which largely combat fatigue and consist of caffeine, energy drinks (typically containing caffeine among other things), nicotine, and other substances, which are covered in the next chapter.

The use of cognitive-enhancing drugs normally coincides with carrying out and completing tasks. We find their use somewhat common among college students. For example, a large survey of college students found that 8.3 percent had used a cognitive-enhancing drug at some point in their lives. In these cases, the use of psychostimulants was considered illicit, as the drugs were not prescribed to the users, and the majority of students reported using a prescription amphetamine (e.g., *Adderall*) (75.8 percent), followed by methylphenidate (24.5 percent), with a small percentage using modafinil (2.6 percent) (Teter et al., 2006). **Figure 6.19** shows the most common reasons given for using a cognitive-enhancing substance from this survey. In addition, among a survey of college students at a university in Germany, 20 percent

**FIGURE 6.19 Reasons for Using Cognitive-Enhancing Drugs**

Results from a survey among high school students (382 students) in order to ascertain reasons for illicitly taking prescription psychostimulant drugs. The survey presented students with a list of potential reasons, and they were allowed to select all that applied.




*Source:* From Teter et al. (2006).

reported using a cognitive-enhancing drug (Dietz et al., 2013), and among Swiss students 16 or older, 9.2 percent reported use of cognitive enhancers (Liakoni, Schaub, Maier, Glauser, & Liechti, 2015).

A number of potential mechanisms of action may account for procognitive effects of stimulants (Bisagno, González, & Urbano, 2016). First, psychostimulant drugs enhance wakefulness and, in that way, improve alertness (Eliyahu, Berlin, Hadad, Heled, & Moran, 2007). Second, psychostimulant drugs elevate dopamine concentrations in the limbic system, which may increase general motor functioning, and also in the prefrontal cortex, which may aid working memory (Goldman-Rakic, Muly, & Williams, 2000). We find this action shared across the psychostimulant drugs. Third, the stimulants modafinil and methylphenidate may exhibit cortical neuroprotection, in that they prevent damage to cells produced by high doses of methamphetamine (toxic to dopamine neurons) (Raineri et al., 2011; Sandoval, Riddle, Hanson, & Fleckenstein, 2003). Fourth, psychostimulants may enhance motivation for engaging in novel stimuli or experiences. This may result in greater and more enduring engagement when studying new material or learning about a new topic (Bromberg-Martin, Matsumoto, & Hikosaka, 2010).

**Review!** Dopamine enhances the motivation to engage with novel stimuli or experiences (Chapter 5).

**Attention deficit hyperactivity disorder (ADHD)** A disorder characterized by inattention, hyperactivity, and inability to control impulsive behaviors

We find drug research and development for cognitive-enhancing drugs aimed at the treatment of neurocognitive disorders. As noted throughout this chapter, psychostimulants represent the primary treatment for **attention deficit hyperactivity disorder (ADHD)**. ADHD consists of a disorder characterized by inattention, hyperactivity, and inability to control impulsive behaviors. The U.S. Centers for Disease Control and Prevention estimates that 6.1 million children (2 to 17 years old) have received an ADHD diagnosis, two-thirds of whom receive treatment. The disorder is more prevalent in boys than girls (Danielson et al., 2018). Among adults, an estimated 4.4 percent meet the diagnostic criteria for ADHD, with the disorder occurring more frequently in men and likely to occur along with another mental disorder diagnosis, such as a substance use disorder, depression, or bipolar disorder (Kessler et al., 2006). Psychostimulants by far represent the pharmacological treatments for ADHD, likely benefiting from the improved attention effects noted above, as well as the rate-dependent effects noted earlier in this chapter. For the rate-dependent effects, we expect that hyperactivity diminishes from psychoactive treatment, just like high response rates become lower in experimental animal studies.

Beyond ADHD, cognitive enhancers have been utilized for dementia. For Alzheimer's disease, the most common approach is an acetylcholinesterase inhibitor, such as donepezil (*Aricept*). As discussed in the next chapter, elevated concentrations of acetylcholine may bestow cognitive benefits by way of the nicotinic receptor system. In the case of Alzheimer's disease, the primary benefits of an acetylcholinesterase inhibitor come from counteracting depleted acetylcholine levels caused by the loss of cholinergic neurons. Otherwise neurologically healthy individuals may find weaker cognitive gains through cholinergic compounds versus psychostimulant drugs.

## STOP & CHECK

1. What is the difference between a cognitive enhancer and a soft cognitive enhancer?
2. How do psychostimulant drugs reduce the symptoms of ADHD?

1. Cognitive enhancers are likely psychostimulant drugs developed for the purpose of treating ADHD, and they act through multiple mechanisms of action to increase cognitive performance. Soft cognitive enhancers tend to act through reducing fatigue and typically consist of caffeinated products or nicotine. 2. Enhanced attention derived from psychostimulant drugs and the ability of these drugs to reduce hyperactivity act to reduce the symptoms of ADHD.

## CHAPTER SUMMARY

Psychostimulant drugs, also called *sympathomimetics*, increase psychomotor and sympathetic nervous system activity and promote alertness and positive mood. Common psychostimulant drugs include amphetamine drugs, cathinones, and cocaine. Many psychostimulant drugs are derived from plants and are produced legally or illegally. Traditionally, the plants containing psychostimulants were used by humans, often through chewing leaves. Psychostimulants such as methamphetamine and cocaine also are prepared in a base form that can be smoked. The salt forms of these drugs can be insufflated or injected. Psychostimulant drugs are administered in many forms, including insufflation, intravenous injection, and inhalation. Among these administration routes, inhalation provides the quickest drug effects. Many psychostimulant drugs have active metabolites that also exhibit psychostimulant effects.

Elevated dopamine levels in the nucleus accumbens account for the reinforcing effects of psychostimulant drugs, and elevated peripheral dopamine and norepinephrine levels account for increased sympathetic nervous system activity. Psychostimulants increase heart rate, blood pressure, body temperature, and other sympathetic nervous system functions. Behaviorally, psychostimulants increase purposeful activity at lower doses and purposeless activity at higher doses. High doses can produce psychotic behavior that resembles positive symptoms in schizophrenia. The subjective effects of psychostimulants include positive mood effects such as increased energy, alertness, and euphoria—and negative mood effects such as anxiousness, agitation, and paranoia. Sensitization occurs for purposeless behavior and for the incentive value of conditioned stimuli during prolonged use of psychostimulants, whereas tolerance occurs for the subjective effects of psychostimulants. Although more men use psychostimulants than women, women may be more likely to become addicted, possibly because of estrogen levels and reactivity to stress.

Pharmacological treatments for psychostimulant addiction either address withdrawal symptoms during abstinence or attempt to prevent relapse. These treatments act on the same sites of actions as psychostimulants such as the tricyclic antidepressant drugs or act through other mechanisms such as those produced by anticonvulsant drugs. Illicit use may also derive from seeking cognitive-enhancing effects of these substances. Such effects also appear beneficial for attention deficit hyperactivity disorder.

## KEY TERMS

Psychostimulants 164
Ephedra (or ma huang) 165
Alkaloid 166
Amphetamines 167
Racemic 167
Cathinone 169

Cocaine 170
Coca paste 170
Freebase 171
Methylecgonidine 176
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CHAPTER 7

# Nicotine and Caffeine

## Chapter Outline

- Nicotine and Tobacco
- History of Tobacco
- Pharmacokinetic Properties of Tobacco
- Nicotine and Nervous System Functioning
- Nicotine's Pharmacological Effects
- Environmental, Genetic, and Receptor Differences Between Light and Heavy Tobacco Users
- From Actions to Effects: Why People Smoke and How They Quit
- Caffeine
- Caffeine Absorption, Duration, and Interaction With Other Psychoactive Drugs
- Caffeine: Antagonist for Adenosine Receptors
- Caffeine: Mild Psychostimulant Effects
- Tolerance and Withdrawal During Sustained Caffeine Use
- From Actions to Effects: Caffeine Habit?

## Learning Objectives

- Describe the forms of tobacco use and types of caffeinated products
- Characterize the pharmacokinetics of nicotine and caffeine
- Describe the pharmacological actions of nicotine and caffeine
- Describe the pharmacological effects of nicotine and caffeine
- Understand the features and treatments of tobacco addiction

In Chapter 6, we considered the most powerful psychostimulants: amphetamines, cathinones, and cocaine. The current chapter covers two less powerful but more often used psychostimulant drugs: nicotine and caffeine.

## Nicotine and Tobacco

**Nicotine**
Central psychoactive ingredient in tobacco

**Nicotine** is the central psychoactive ingredient in tobacco. Tobacco consists of leaves from plants in the genus *Nicotiana*, grown in South and North America (**Figure 7.1**). The most popular plant used commercially is *Nicotiana tabacum*, leading to the name "tobacco." This plant species produces greater amounts of nicotine than other *Nicotiana* species (Saitoh, Noma, & Kawashima, 1985). Traditional forms of smoking tobacco consist of rolled tobacco leaves, and modern versions consist of cigars and cigarettes. When tobacco is chewed or smoked, small nicotine-containing tobacco particles called *tar* and other tobacco chemicals enter the body.

**FIGURE 7.1 Tobacco Plants**

Nicotine is the central psychoactive constituent in tobacco plants.

iStockphoto/Praiwun

Cigarettes are the most commonly used tobacco product. A **cigarette** is composed of a tobacco blend rolled in a thin sheet of paper. Many cigarettes contain a filter of cellulose acetate that reduces the amount of tobacco tar inhaled. The tobacco portion of a regular cigarette is approximately 60 mm (2.25 in.) in length, and filtered cigarettes have a 25 mm (~1 in.) filter and usually a shorter length of tobacco. Depending on the size and blend, a cigarette contains approximately 10 mg of nicotine, but a user inhales 1–2 mg of nicotine in tobacco smoke (Connolly, Alpert, Wayne, & Koh, 2007). Some brands of cigarettes have a flavoring added, the most popular of which is menthol. Menthol cigarettes, in particular, are almost exclusively used by African Americans, and more women tend to use menthol cigarettes than men (Muscat, Richie, & Stellman, 2002).

**Cigarette**
A tobacco blend rolled in a thin sheet of paper

**Cigars** consist of tightly rolled bundles of dried tobacco leaves wrapped in a leaf. Cigars vary widely in diameter, length, and nicotine content. For example, a Winchester Little Cigar is 8 mm (~ ⅓ in.) in diameter and 60 mm (2⅓ in.) long, whereas a Cuesta-Rey No. 1 is 20 mm (~ ¾ in.) in diameter and 211 mm (8⅓ in.) in length. A Winchester Little Cigar contains 5.9 mg of nicotine, and a Cuesta-Rey No. 1 cigar contains 335.2 mg of nicotine (Henningfield, Fant, Radzius, & Frost, 1999).

**Cigar**
Tightly rolled bundle of dried tobacco leaves wrapped in a leaf

*Pipe smoking* consists of inhaling smoke from a tobacco blend. For a water pipe, a user inhales smoke that has passed through a container of water. Hookah water pipe smoking is increasingly prevalent among younger Western adults, although it has been a common method of smoking in the Middle East for centuries (Neergaard, Singh, Job, & Montgomery, 2007) (**Figure 7.2**). A typical **hookah** is an ornately shaped and decorated water pipe assembly consisting of a charcoal-heated, tobacco-holding chamber pipe connected through the water jar mouth and into the water; smokers inhale tobacco smoke from a hose projecting from the top of the jar. Inhaled tobacco smoke first passes through a bowl of water. Many users believe that this method reduces the harmful effects of tobacco, although studies of water pipe tobacco exposure state otherwise (Ahmed, Jacob, Allen, & Benowitz, 2011; Jacob et al., 2011).

**Hookah**
An ornately shaped and decorated water pipe assembly consisting of a charcoal-heated, tobacco-holding chamber pipe connected through the water jar mouth and into the water, with tubes from the jar allowing for tobacco smoke inhalation

**Smokeless tobacco** products consist of any tobacco form intended for absorption in the mouth. Products called *chew*, *snuff*, and *dipping tobacco* consist of a tobacco blend that a user either chews or pockets in his or her cheek. When the product is spent, users spit the tobacco out. Another type is *snus*, which consists of a ground tobacco-leaf powder packaged in tea bag-like pouches that can be disposed of without spitting. Snus users typically keep the pouch between their gums and upper lip (Digard, Errington, Richter, & McAdam, 2009).

**Smokeless tobacco**
A tobacco form intended for absorption in the mouth

**Dissolvable tobacco** provides oral delivery of nicotine through a product that dissolves in the mouth, such as a lozenge, strip, or stick. Nicotine lozenges are generally used for the purpose of quitting smoking. Sweetened strips or sticks were mostly developed for smokers who are not conveniently able to smoke due to smoking bans in public places. Dissolvable tobacco products contain amounts of nicotine similar to those found in cigarettes. The resemblance of these products to candy created an exposure risk for kids and also concerned regulators, who believed that marketing appeared attractive to adolescents. Such products are largely unavailable today (Connolly et al., 2010).

Finally, **e-cigarettes** (or **electronic nicotine delivery systems**)—electronic nicotine vaporizers often shaped like cigarettes—have emerged as another popular

**E-cigarettes (or electronic nicotine delivery systems)**
Electronic nicotine vaporizers often shaped like cigarettes

**FIGURE 7.2 A Hookah**

A water pipe or *hookah* is traditionally used for smoking tobacco and is increasingly used among young Western adults.

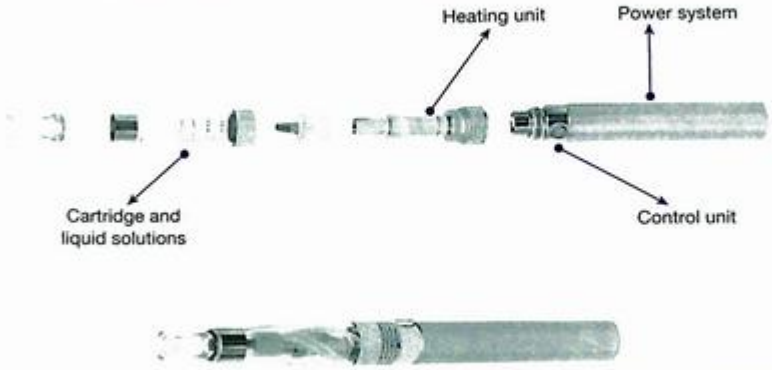
*Source:* iStockphoto/spilman.

form of nicotine delivery. Modern e-cigarettes contain a battery that powers a heater attached to an *atomizer*, a component that reduces liquid into a fine spray. A liquid cartridge containing nicotine, propylene glycol, and vegetable glycerin plugs into the atomizer, which vaporizes the liquid when a sensor detects airflow passage or when the user presses a button (Trtchounian, Williams, & Talbot, 2010) (**Figure 7.3**). Thus, a user inhales a nicotine vapor solution through an e-cigarette. Vegetable glycerin, and other compounds that might be added to an e-liquid, makes the vapor visible when exhaled.

E-cigarettes once were used as a cigarette cessation approach—that is, they somewhat had the feel of a cigarette, but the user inhaled vaporized nicotine rather than tar particles from tobacco. These first-generation e-cigarettes closely resembled traditional cigarettes. Thus, we could describe those e-cigarette users as "smokers" who were attempting to quit smoking traditional cigarettes. Today, many

**FIGURE 7.3 An Electronic Cigarette**

Electronic cigarettes (commonly known as an "e-cigarettes") vary in style and components, but all have a power system, control unit, heating unit, atomizer, and an attachment for a liquid cartridge.




Source: iStockphoto/-zlaki-.

e-cigarette liquid cartridges also include flavorings, such as fruit, candy, or menthol flavors. Fruit and mint flavorings were popular in adolescents according to one survey of users of the e-cigarette product JUUL (Leventhal et al., 2019).

Users can assemble their e-cigarettes using customized components (or "mods"). For example, a user can add a mod to adjust the level of power to the heater, with greater heat leading to more e-liquid vaporized, and vice versa (Farsalinos et al., 2014). These second-generation e-cigarettes seldom resemble actual cigarettes; instead, they have metallic, sleek-looking designs (Farsalinos et al., 2014). These devices tend to be referred to as *personal vaporizers*, "*vape pens*," or similar names. The amount of nicotine found in most second-generation e-cigarette liquid cartridges varies from 20 to 40 mg/ml (Davis, Dang, Kim, & Talbot, 2015). However, the actual amount of nicotine in vapor inhaled by users varies greatly, depending on how the user inhales the vapor (e.g., fullness and frequency on inhalation) and the settings on the device. With these considerations in mind, inhaled nicotine from e-cigarettes may vary from 0.3 mg to over 4 mg of nicotine, based on a study evaluating nicotine yield for 15 puffs from a variety of ways a user might puff an e-cigarette (Talih et al., 2015). Further, users of second-generation e-cigarettes may not be current or former tobacco smokers, leading us to identify them as "vapers" rather than smokers. Thus, a person using a nicotine vaporizer is "**vaping**" rather than smoking (Fagerstrom, Etter, & Unger, 2015).

**Vaping**
Inhaling vapor from an e-cigarette

Tobacco use is widespread. In 2017, approximately 19 percent of Americans ages 18 and older reported as current cigarette smokers (Wang et al., 2018). However, cigarette use in the United States has steadily declined since the 1960s. According

to the World Health Organization, tobacco smoking is high in many parts of Europe and Asia and throughout Central and South America. Asia includes the highest rates. More than 60 percent of males in the Russian Federation and China use tobacco products. Males generally use tobacco products more than females, but these differences vary across countries. For example, equal smoking rates occur among males and females in Norway and Sweden, whereas fewer than 10 percent of females smoke in the Russian Federation and China (Mackay & Eriksen, 2002).

While we find a decline in cigarette smoking, we see an increasing trend in nicotine vaping. The percentage of a large sample of U.S. adults who ever used an e-cigarette rose from 3.3 percent in 2010 to 8.5 percent in 2013; among chronic smokers, e-cigarette use rose from 1.1 percent in 2010 to 18.4 percent in 2013 (King, Patel, Nguyen, & Dube, 2014; Rigotti et al., 2015). Among middle and high school students, 6.1 percent had reported ever using e-cigarettes between the years 2011 and 2013 (Bunnell et al., 2014). In 2017, 2.8 percent of adults 18 or older reported as current e-cigarette users (Wang et al., 2018). However, lack of agreement on what to actually call an e-cigarette may impact the accuracy of survey results. For example, when Morean and colleagues (2018) surveyed a large sample of high school students on use of specific devices or different terms for use, rather than simply using the term "e-cigarette," nearly 35.8 percent reported using an e-cigarette at least once.

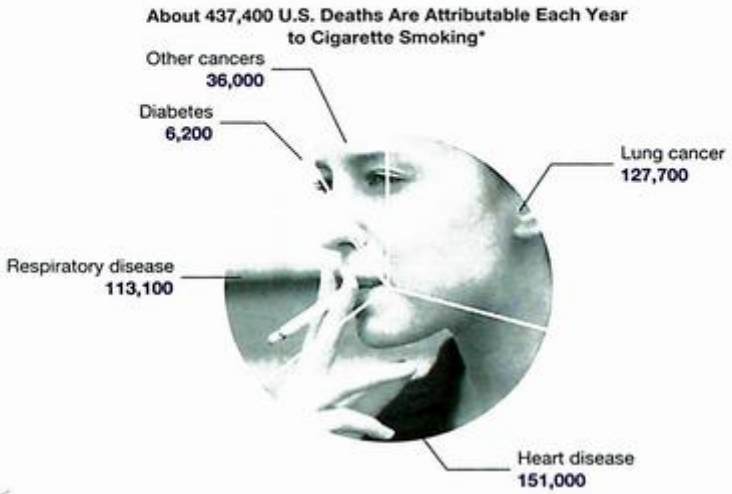
Tobacco use has serious health effects. The three primary causes of tobacco-related death each year are cancer, pulmonary disease, and cardiovascular disease. According to the U.S. Centers for Disease Control and Prevention, an estimated 437,400 deaths among firsthand tobacco smokers occurred each year between 2005 and 2009. Of those deaths, most resulted from at least one of these three conditions, with lung cancer being the leading cause of tobacco-related deaths (**Figure 7.4**). African Americans have greater mortality rates from smoking, despite smoking less than European Americans, because of greater incidence of these smoking-related diseases (Fiore et al., 1989).

Evidence of adverse effects from e-cigarette use varies across scientific studies. The most consistent finding is that most e-cigarette vapors contain volatile organic compounds, including toluene and xylene. Otherwise, conflicting studies have been shown for a variety of compounds or material capable of negatively impacting health, including organic compounds (e.g., formaldehyde, acetaldehyde) and particulate matter in e-cigarette vapor. Vapor exposure has the potential to cause cytotoxity (i.e., damage to cells) (Pisinger & Døssing, 2014). In particular, these vapors contain metallic nanoparticles and glass particle fibers that have the potential to damage cells in lung tissue (Lerner et al., 2016; Shin et al., 2018). Reports also exist for lung injury potentially caused by vitamin E acetate, a chemical harmful to tissue when heated and vaporized.

In addition to these harmful chemicals, solutions used in e-liquids may lead to lipid-related lung injuries (Eissenberg & Maziak, 2020). These injuries occur when fatty acids accumulate in the lungs, causing inflammation. Heating e-liquids that commonly contain vegetable glycerin, which is rich in vegetable fatty acids, aerosolizes fatty acids for inhalation in the lungs. Between the exposure to harmful chemicals and the risk of lipid-related lung injury, dozens of deaths associated with e-cigarette use have occurred in the United States due to lung injuries (Balmes,

**FIGURE 7.1 Firsthand Smoking-Related Deaths**

Lung cancer, chronic obstructive pulmonary disease such as emphysema, and heart disease are the greatest causes of death associated with tobacco use.




*Average annual number of deaths, 2000–2004.

*Source:* MMWR 2008; 1226–1228. Photo: Copyright iStockphoto/Kuzma.

2019). While lung conditions occur in tobacco smokers after many years of regular use, we find that lung-related deaths among vapers occurred after only a few years of use.

Secondhand smoke exposure also increases one's risk to negative health effects. **Secondhand smoke** consists of smoke exhaled from a smoker or smoke released from a burning tobacco product (i.e., a lit cigarette or cigar). Between 2005 and 2009, this form of tobacco exposure accounted for 7,333 annual deaths from lung cancer and 33,951 annual deaths related to coronary heart disease. Secondhand smoke exposure also accounted for 400 sudden infant death syndrome incidents in each year during that same period. We also link secondhand smoke to health effects in children, where we find greater incidence of asthma, bronchitis, pneumonia, and ear infections (U.S. Department of Health and Human Services, 2014).

A nonsmoker may also be exposed to thirdhand smoke. **Thirdhand smoke** consists of remnants from tobacco smoking gathered on material in the smoker's local environment after smoking has finished (Winickoff et al., 2009). A nonsmoker may be exposed to tobacco products that cling to hair, skin, or clothing, and these products can remain on fabrics for months after smoking ceases (Bahl et al., 2016).

**Secondhand smoke**
Smoke exhaled from a smoker or smoke released from a burning tobacco product

**Thirdhand smoke**
Remnants from tobacco smoking gathered on material in the smoker's local environment after smoking has finished

Tobacco products from smoke gather on walls, flooring, and various objects in the setting, making these other sources of exposure for nonsmokers. Young children, in particular, may ingest this material from playing on the floor or putting objects in their mouths, and samples from hand swabs from children of smokers reveal detectable levels of nicotine. The saliva from children exposed to thirdhand smoke also contains nicotine's metabolite cotinine, indicating absorption of nicotine occurs from exposure to environmental nicotine (Mahabee-Gittens, Merianos, & Matt, 2018). Thirdhand smoke effects are a relatively new area of research, and potential health effects from this exposure have yet to be found. So far, researchers have found cytotoxic chemicals deposited from thirdhand smoke as well as chemicals that inhibit cell proliferation (Bahl et al., 2016). These findings suggest that a risk of adverse effects occurs from exposure to thirdhand smoke.

## History of Tobacco

The discovery of fossilized leaves of *Nicotiana tabacum* in Peru suggests that tobacco existed at least 2.5 million years ago. Indigenous peoples in the Americas, including the Mayas, Incans, Toltecs, and Aztecs, smoked tobacco as part of their religious practices. In religious ceremonies, tobacco was smoked to achieve a trance-like state (**Figure 7.5**).

**FIGURE 7.5** **Ancient Tobacco Use**

Tobacco was smoked by ancient Mayan priests for ceremonial purposes.

Shutterstock/Jef Thompson

Religious practices remained the primary use of tobacco until Europeans discovered tobacco during Columbus's 1492 expedition. After Columbus landed in the Bahamas, the native Arawak gave dried tobacco leaves as a gift to the explorer. Not realizing the significance of the tobacco leaves to the Arawak, Columbus simply discarded them. A few days later, however, Columbus noted that the leaves had "high value among [the Arawak]" (Brecher, 1972; Gately, 2001).

Rodrigo de Jerez, a member of Columbus's expedition, participated in the native practice of rolling tobacco leaves and smoking them. Thus, Jerez became the first European to smoke tobacco. In fact, he became a habitual user and brought back a large personal tobacco supply to Spain. Yet, the frightening sight of tobacco smoke coming from his mouth and nose brought him to judgment by the holy inquisitors, who imprisoned him for seven years (Gately, 2001).

Use of tobacco in Europe soon grew. By the mid-16th century, tobacco was a widely traded commodity. Complaints against tobacco also grew. The first medical concern against using tobacco was published in the early 17th century, which compared the deleterious health effects of chimney sweeps to those of tobacco smokers. In 1610, Sir Francis Bacon noted the difficulty in quitting tobacco use. In 1634, Russian Tsar Michael I decreed that a first offense for tobacco use was punishment by whipping and transport to Siberia; the second offense was death (Brecher, 1972). Although a severe response, the decree reflected the sentiments of many that tobacco led to nothing good (Doll, 1998). In 1612 Jamestown, John Rolfe raised the first European tobacco crop for commercial use, marking the beginning of a thriving American industry that remains active today. Nearly 200 years later, in 1809, Louis Nicolas Vanquelin isolated nicotine as a key ingredient in tobacco.

While regulations over tobacco marketing and use largely appear over the last couple of decades, we find tobacco's deleterious effects on health documented for centuries. The first scientific report linking tobacco to cancer might be from Sommering in 1795 Germany, who noted cancer of the mouth among tobacco users. Since about this time, physicians have generally understood the links between tobacco use and cancer as well as overall poor health (Doll, 1998).

The beginning of the 20th century marked a renewed study of tobacco's adverse health effects. Early in this century, scientists studied the effects of tobacco and cancer in animals. In 1938, a study by Raymond Pearl reported that heavy smokers lived a shorter life than nonsmokers (Gately, 2001). Many groups during this time formed antitobacco societies, which largely became associated with the alcohol temperance movement. As such, the success of the antitobacco movement fell away with the public's turn against alcohol prohibition (Doll, 1998). By the 1990s, the health risks of tobacco had become well characterized and widely publicized. The heavy marketing and advertising of cigarettes along with the increasing public health burden from tobacco use culminated in numerous lawsuits and congressional involvement to regulate the tobacco industry. In 1994, the U.S. Congress held tobacco hearings that included the testimony of seven tobacco company CEOs. The CEOs stated that nicotine was not an addictive substance. By 1998, lawsuits concerning violations of consumer protection and antitrust laws filed against four major U.S. tobacco companies—Philip Morris Inc., R.J. Reynolds, Brown & Williamson, and Lorillard—by state attorneys general led to the Tobacco Master Settlement

Agreement. The agreement partially reimbursed states for health costs of tobacco use and led to changes in the marketing and advertising of tobacco products. Today, tobacco products must include special health warning labels, but the products are still sold legally throughout the world.

## STOP & CHECK

1. What is the key psychoactive ingredient in tobacco?
2. Among the many forms of tobacco, which product remains the most used?
3. What is the greatest cause of death from smoking?
4. In which American colony was the first tobacco crop grown?

1. nicotine 2. cigarettes 3. lung cancer 4. Jamestown

## Pharmacokinetic Properties of Tobacco

### Tobacco Use and Nicotine Absorption

**Flue curing**
Venting heat through a metal flue onto tobacco leaves

Tobacco use consists of inhaling or chewing tobacco blends or other products. Smoked tobacco was seldom inhaled into the lungs prior to the common practice of flue-curing tobacco blends in cigarettes in the early 1900s. **Flue curing** consists of venting heat through a metal flue onto tobacco leaves. The process reduces the pH of smoke toward neutral (i.e., closer to pH = 7.0) by converting starches to sugars, making the smoke less harsh and irritating to inhale. Cigars instead use air-dried tobacco leaves, retaining an alkaline pH and having fewer sugars. As a result, cigar smokers may be less likely to inhale tobacco smoke into their lungs than cigarette smokers. Cigarette smokers who also smoke cigars, however, do tend to fully inhale cigar smoke into their lungs (Turner, Sillett, & McNicol, 1977).

### Nicotine Absorption Through Lung and Oral Tissues

A typical cigarette user consumes 13 cigarettes per day, although smokers who repeatedly attempt to quit smoking tend to smoke between 20 and 40 cigarettes per day (Shiffman, 1989). In general, though cigarette smokers tend to inhale smoke into their lungs more often than cigar smokers do, cigar smokers absorb more nicotine than cigarette smokers. Greater nicotine absorption from cigars likely occurs from nicotine absorption through mucous membranes in the mouth (Turner et al., 1977). For e-cigarettes, Farsalinos and colleagues (2014) found that newer devices lead to 70 percent greater nicotine levels in plasma than first-generation devices, and that nicotine absorbed from new-generation devices reaches levels similar to traditional cigarettes.

When smoking tobacco, **tar**, the particulate matter produced from burning tobacco, adheres to tissues in the mouth, nose, throat, and, if fully inhaled, the lungs. When exhaled, tar also adheres to the skin. Nicotine and many other chemicals leach from the tar and onto tissue the tar makes contact with. For vaporized e-liquids, nicotine disperses in liquid droplets containing water and constituents released from the e-liquid, which might include metals or glass fibers, as noted earlier (Grana, Benowitz, & Glantz, 2014). All tissue sites provide a means of absorption. Given the large surface area of the lungs, inhaled tobacco smoke or e-liquid vapor provides the most effective route of nicotine administration.

**Tar**
Particles released from burning tobacco

The freebase form of nicotine is lipid soluble, allowing for absorption through mucous membranes in the mouth. The greatest amount of freebase nicotine that can be absorbed is 50 percent, which occurs at a pH of 8.02. As pH levels deviate from 8.02, the percentage of freebase nicotine decreases. Many smokeless and dissolvable tobacco products offer pH values close to 8.02, as shown for dissolvable nicotine products in **Table 7.1** (Djordjevic, Hoffman, Glynn, & Connolly, 1995; Henningfield, Radzius, & Cone, 1995; Rainey, Conder, & Goodpaster, 2011). The majority of e-cigarette liquids have pH values between 7.0 and 9.0, leading to greater than 50 percent of freebase nicotine for many of these products (Lisko, Tran, Stanfill, Blount, & Watson, 2015).

When inhaling tobacco smoke, the acidity of smoke from a cigarette reduces saliva to a pH less than 6.0, reducing the amount of freebase nicotine available for absorption in the mouth (Armitage & Turner, 1970). However, tobacco companies do add ammonia-forming compounds to tobacco blends, which increases the amount of freebase nicotine (Pankow et al., 1997). Smoke from cigars tends to have pH levels closer to 7.0, although the pH levels vary considerably, depending on the size of the cigar and part of the cigar smoked (Henningfield et al., 1999). The pH levels for cigars therefore favor greater nicotine absorption in the mouth. This can mean significant nicotine absorption for many cigar smokers who do not fully inhale tobacco smoke, as noted earlier.

Most tobacco products result in blood nicotine concentrations of 12 to 16 nanograms[1] per milliliter, although absorption times vary. Peak absorption

**TABLE 7.1 pH and Percentage Free Nicotine in Selected Dissolvable Camel Tobacco Products**

| Camel Brand | pH | Percentage Free Nicotine |
|---|---|---|
| Mellow Orb | 7.82 | 38.5 |
| Fresh Orb | 7.1 | 28.0 |
| Mellow Stick | 7.51 | 23.5 |
| Fresh Strip | 8.02 | 50.2 |

*Source:* Adapted from Rainey et al. (2011).

[1]A nanogram is one billionth, or $10^{-9}$, of a gram.

for nicotine from cigarettes occurs after approximately seven minutes. Nicotine absorption times through oral mucous membranes tend to peak between 20 and 30 minutes after introduction (Henningfield & Keenan, 1993; Vansickel et al., 2010). Peak nicotine absorption from e-cigarettes, from either first- or new-generation devices, occurs after 30 minutes, suggesting that most nicotine absorption occurs through mucous membranes in the mouth, rather than lungs (Farsalinos et al., 2014).

In addition to the speed of nicotine delivery, tobacco smoking or vaping provides users the ability to adjust the amount of nicotine absorbed. A smoker accomplishes these adjustments by varying the number of inhalations, duration of an inhalation, completeness of inhalation, and the number of cigarettes smoked (Frederiksen, Martin, & Webster, 1979). Overall, we refer to these characteristics as *puff topography*. Puff topography impacts the amount of nicotine inhaled when vaping, and vapers can adjust a nicotine vaporizer's heating level to alter the amount of nicotine inhaled as well.

## Distribution and Biotransformation of Nicotine

**Cotinine**
Active metabolite of nicotine

Once absorbed, nicotine readily passes through the blood–brain barrier. In the liver, CYP-2A6 enzymes metabolize 80–90 percent of nicotine, producing the active metabolite **cotinine**, which exhibits pharmacological actions similar to nicotine. Slower metabolism occurs for mentholated versus non-mentholated cigarettes (Benowitz, Herrera, & Jacob, 2004).

Genetic polymorphisms influence CYP-2A6 activity levels. CYP-2A6*4, *7, and *9 polymorphisms exhibit reduced CYP-2A6 activity, causing slower metabolism of nicotine to cotinine. In other words, nicotine levels remain higher in the body because of reduced metabolism. These polymorphisms are prevalent within Asian populations. Individuals who exhibit homogenous mutant forms of these gene polymorphisms or heterogeneous mutant forms that have a combination of the *4, *7, or *9 polymorphisms tend to be light smokers and have a lower risk of tobacco-related health effects (Ariyoshi et al., 2002; Minematsu et al., 2006; Yusof & Gan, 2009). African Americans exhibit a slower metabolism of nicotine, engendering a longer period of time for intact nicotine to exert pharmacological effects (Pérez-Stable, Herrera, Jacob, & Benowitz, 1998). This may be due to a preference by African American smokers for using mentholated cigarettes.

## Elimination of Nicotine

The half-life for nicotine is approximately two hours, but this clearance time depends on a smoker's status. Chronic smokers have a 30-percent faster elimination rate of nicotine than nonsmokers. These findings suggest that chronic tobacco use sensitizes pharmacokinetic processes for nicotine (Perkins et al., 1994). The half-life for cotinine is approximately 17 hours (Pérez-Stable et al., 1998). Both nicotine and cotinine are primarily eliminated from the body through urine, and so a simple urine analysis for cotinine can reveal tobacco use more than a day later.

## STOP & CHECK

1. Why is inhalation the most effective route for absorbing nicotine from tobacco tar?
2. What factors influence nicotine's ability to be absorbed in the mouth?
3. What is the active metabolite for nicotine?

1. The lungs have a large surface area that helps speed delivery of nicotine to the brain after blood absorption. The large surface area also overcomes the poor absorption of nicotine when delivered in tobacco smoke, which has a less-than-ideal pH of approximately 6. 2. The freebase form of nicotine absorbs through mucous membranes in the mouth. The most ideal pH for absorption in the mouth is 8.02. Thus, nicotine products producing similar pH levels will be conducive to nicotine absorption through mucous membranes. 3. cotinine

## Nicotine and Nervous System Functioning

Nicotine functions as an agonist for cholinergic nicotinic receptors (**Figure 7.6**). Cotinine, the active metabolite of nicotine, serves as a weak agonist for nicotine receptors. When a nicotinic receptor agonist binds to these receptors, a conformational change takes place, opening a channel for positively charged ions, such as $Ca^{2+}$, $Na^{+}$, and $K^{+}$. Some ions pass more readily through nicotinic receptor channels than others. For example, $\alpha_7$ receptors are most permeable for $Ca^{2+}$ ions (Séguéla, Wadiche, Dineley-Miller, Dani, & Patrick, 1993).

**Review!** Nicotinic receptors are ionotropic and comprise α and β subunits. Nicotinic receptors can include other subunit types as well, which are denoted by different Greek symbols. The configuration of these subunits defines each receptor's name (Chapter 3).

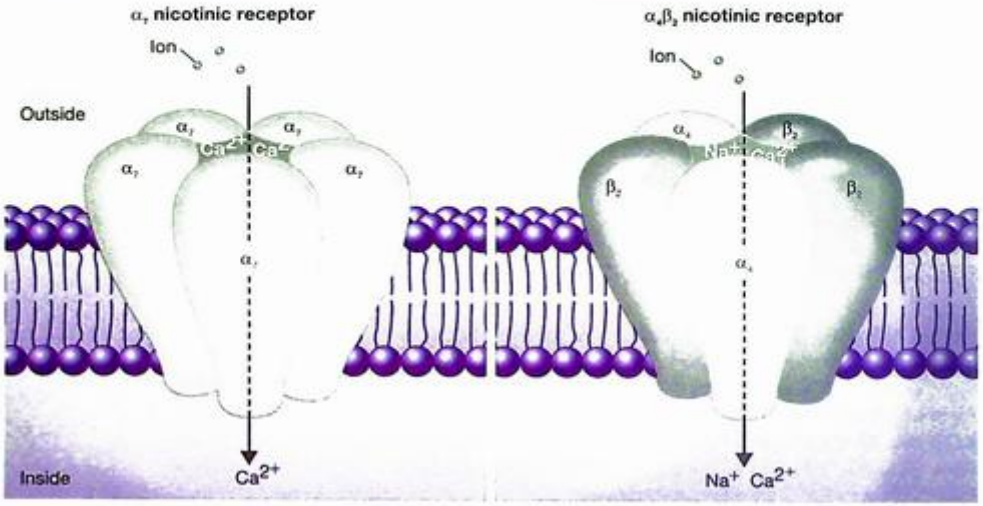
A short time after nicotine (or another agonist) activates a nicotinic receptor, the receptor enters a desensitized state, which limits the duration of action for nicotine's acute pharmacological effects (**Figure 7.7**) (Fenster, Rains, Noerager, Quick, & Lester, 1997; Hsu, Amin, Weiss, & Wecker, 1996). During the desensitized state, the channels close and the receptors cannot be activated. These receptors enter this desensitized state even when the receptors remain bound by an agonist. After a period of time, the desensitized state ends and the receptors can again be activated by an agonist.

**Functional antagonism**
An indirect or atypical means of inhibiting a receptor's activity, such as when the net effects of a receptor agonist consist of a longer inactivated receptor state and a shorter activated receptor state

Because of desensitization, agonists cause nicotinic-receptor channels to remain closed *longer* than they are open. In this way, nicotinic-receptor agonists also produce **functional antagonism**, meaning that nicotine causes these receptors to have a longer inactivated state than an activated state. Thinking of nicotine as a *functional antagonist* is useful for understanding changes in nicotinic receptors during chronic nicotine administration. During such administration, the brain compensates

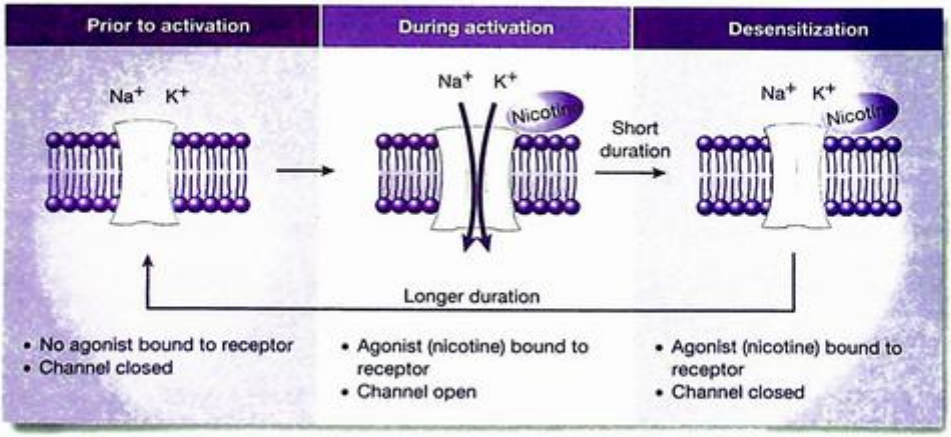
## FIGURE 7.6 Nicotinic Receptors

Each nicotinic ionotropic receptor comprises a configuration of α and β subunits.




## FIGURE 7.7 Nicotinic Receptor Desensitization

When bound to by an agonist, nicotinic receptors undergo an active state and then a desensitized state. The receptor cannot be activated during the desensitized state, and the desensitized state occurs for a longer period of time than the active state.



for the repeated closing of nicotinic-receptor channels by *upregulating* nicotinic receptors (Schwartz & Kellar, 1985; Wonnacott, 1990). **Upregulation** refers to an increased production of proteins.

**Upregulation**
Increased production of proteins

Both the central and peripheral nervous systems contain nicotinic receptors. Peripherally, nicotinic receptors are located postsynaptically on neuromuscular junctions in the somatic nervous system. Within neuromuscular junctions, the activation of $\alpha_1\beta_1\delta\gamma$ nicotinic receptors on muscle fibers causes muscles to contract.

Nicotinic receptors are located in ganglia of the autonomic system, including both the sympathetic and the parasympathetic nervous systems. Of these two systems, the activation of nicotinic receptors primarily increases sympathetic nervous system activity (Li, LaCroix, & Freeling, 2009). Different subtypes of nicotinic receptors are likely involved in the sympathetic and parasympathetic systems. For cardiovascular effects, Li and colleagues (2009) discovered that $\alpha_7$ receptors activate the parasympathetic nervous system, whereas $\alpha_4\beta_2$ receptors activate the sympathetic nervous system.

**Review!** The autonomic nervous system includes the sympathetic nervous system, which increases physiological activity, and the parasympathetic nervous system, which decreases physiological activity (Chapter 2).

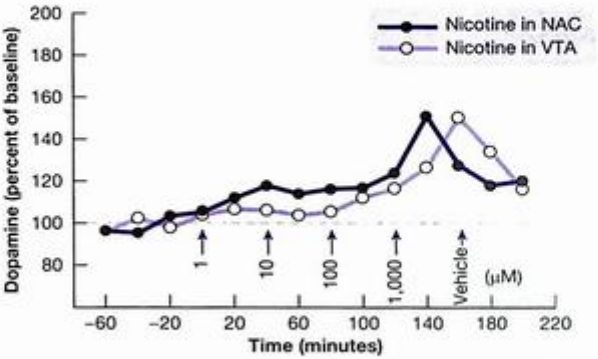
Nicotinic receptors are found throughout the central nervous system and play an important role in many nervous system processes. The cerebral cortex and hippocampus, two brain areas important for cognitive functioning, highly express both $\alpha_4\beta_2$ and $\alpha_7$ nicotinic receptors. High amounts of $\alpha_4\beta_2$ nicotinic receptors are also found in the basal ganglia, an area important for regulating movement, and the substantia nigra, the source of dopamine neurons that terminate in the basal ganglia. In the dopamine reward pathway, the ventral tegmental area contains $\alpha_4\beta_2$ and $\alpha_6\beta_2$ receptors, and the nucleus accumbens also contains $\alpha_4\beta_2$ receptors (Brunzell, 2012; Yang et al., 2011; Zhao-Shea et al., 2011).

The activation of nicotinic receptors in either the ventral tegmental area or the nucleus accumbens increases dopamine release in the nucleus accumbens. Researchers discovered these effects using microdialysis techniques in animals (see Box 3.1). For example, Nisell and colleagues (1994) infused nicotine into either the ventral tegmental area or the nucleus accumbens in rats. Microdialysis probes in these structures collected cerebrospinal fluid samples for dopamine analysis. The infusion of nicotine in the ventral tegmental area produced a large, sustained increase in dopamine levels in the nucleus accumbens. When infused into the nucleus accumbens, nicotine produced a much shorter increase in dopamine levels in the nucleus accumbens (**Figure 7.8**). Based on these findings, nicotine acts in both areas to elevate dopamine levels in the nucleus accumbens, but nicotine's actions in the ventral tegmental area are especially effective for inducing dopamine release in the nucleus accumbens.

In addition to enhancing the release of dopamine in the brain, the activation of nicotinic receptors influences many other neurotransmitters in the brain, including acetylcholine, glutamate, GABA, norepinephrine, serotonin, and the hormone vasopressin. These widespread interactions preclude identifying highly specific roles

**FIGURE 7.8** **Nicotine Increases Dopamine Levels in the Nucleus Accumbens**

Infusion of nicotine into either the ventral tegmental area (empty circles) or the nucleus accumbens (filled circles) increases dopamine release in the nucleus accumbens.




*Source:* Nisell, M., Nomikos, G. G., and Svensson, T. H. (1994). Infusion of Nicotine in the Ventral Tegmental Area or the Nucleus Accumbens of the Rat Differentially Affects Accumbal Dopamine Release. *Pharmacology & Toxicology, 75*: 348–352. doi:10.1111/j.1600-0773.1994.tb00373.x. John Wiley & Sons Ltd.

that nicotinic receptors have on behavior. Clearly, by acting on nicotinic receptors, nicotine and other nicotinic-receptor agonists have diverse effects on the central nervous system.

Beyond nicotine, other compounds in tobacco may act in the nervous system, possibly enhancing nicotine's effects. In particular, many chemicals in tobacco inhibit $MAO_A$ and $MAO_B$ activities, including the compounds 2,3,6-trimethyl-1,4-naphthoquinone, 2-naphthylamine, harman, and norharman (Hauptmann & Shih, 2001; Herraiz & Chaparro, 2005; Khalil, Steyn, & Castagnoli, 2000).

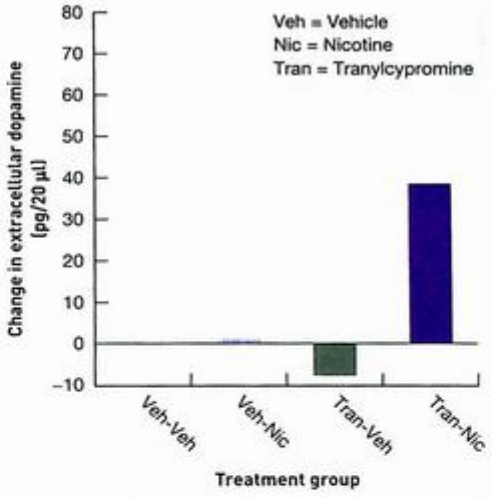
These actions may explain why long-term smokers exhibit a decreased activity of $MAO_A$ and $MAO_B$ enzymes (Fowler et al., 1996a, 1996b). MAO inhibition also enhances the effects of nicotine on dopamine levels in the nucleus accumbens. In a microdialysis study conducted by Lotfipour and colleagues (2011), rats treated with both nicotine and tranylcypromine, an $MAO_{A/B}$ reuptake inhibitor, exhibited a substantially greater increase in nucleus accumbens dopamine levels than rats treated with either drug alone (**Figure 7.9**).

**Review!** Monoamine oxidase (MAO) is an enzyme that breaks down, or catabolizes, dopamine, norepinephrine, and serotonin (Chapter 3).

Acetaldehyde, a common ingredient in tobacco, may also enhance nicotine's effects in the brain. In a study using rats in a self-administration procedure, treatment with

**FIGURE 7.9** **MAO Inhibition Enhances Nicotine's Effects on Dopamine Release**

Rats treated with both nicotine and tranylcypromine, an MAO reuptake inhibitor, exhibited a substantially greater increase in nucleus accumbens dopamine levels than rats treated with either drug alone.




*Source:* Data from Lotfipour et al. (2011).

acetaldehyde increased self-administration of nicotine, suggesting that acetaldehyde increased nicotine's rewarding effects (Belluzzi, Wang, & Leslie, 2005). In particular, these effects occurred in juvenile, but not adult, rats, suggesting that adolescence is a particularly vulnerable time for acquiring an addiction to nicotine.

## STOP & CHECK

1. At nicotinic cholinergic receptors, nicotine functions as a(n) _____.
2. Nicotine causes an increase in dopamine release in the nucleus accumbens by acting on nicotinic receptors in the nucleus accumbens and the _____.
3. What is another compound in tobacco that may facilitate nicotine's effects?

1. agonist 2. ventral tegmental area 3. an MAO inhibitor

## Nicotine's Pharmacological Effects

Nicotine produces physiological, behavioral, and subjective effects, and tobacco, the main source of nicotine, produces a host of adverse effects. When characterizing the pharmacological effects of nicotine, researchers understand that the length of nicotine use is important. Because upregulation of nicotinic receptors occurs during repeated administration, the acute effects of nicotine can differ from the chronic effects of nicotine. Thus, the effects of nicotine on a first-time smoker can differ greatly from the effects of nicotine on a long-time smoker.

### Nicotine's Effects on Cardiovascular Function and Appetite

Nicotine produces widespread physiological effects. The two most notable are on the cardiovascular system and appetite. In both smokers and nonsmokers, nicotine produces cardiovascular effects consisting of increases in heart rate and blood pressure. Because these effects are observed in smokers, a tolerance to these effects does not occur during chronic nicotine administration.

**Acute tolerance**
Decreased responsiveness to a drug's effects after a single administration of the drug

Acute tolerance occurs for a number of nicotine physiological effects. **Acute tolerance** refers to decreased responsiveness to a drug's effects after a single administration of the drug. Acute tolerance to nicotine's effects on heart rate and blood pressure happens when nicotine is administered soon after the previous administration (Perkins et al., 1994). Acute tolerance occurs partly because the subsequent nicotine administration occurs while many nicotinic receptors remain in a desensitized state.

Most smokers experience acute tolerance every morning. Nicotine delivered from the first cigarette of the day causes an increase in heart rate and blood pressure. The next cigarette exhibits weaker effects on heart rate and blood pressure. Because of acute tolerance, heart rate and blood pressure soon return to normal levels.

Nicotine reduces appetite in both non-tobacco users and long-term smokers. In a study by Perkins and colleagues (1991), nicotine was administered to either non-tobacco users or smokers who had not smoked since the night before. In both groups, nicotine reduced self-reported hunger and the number of snack foods consumed during the testing sessions (**Figure 7.10**). The appetite-suppressing effects of nicotine contribute to weight loss in many tobacco users, and tobacco users often cite potential weight gain as a reason not to quit.

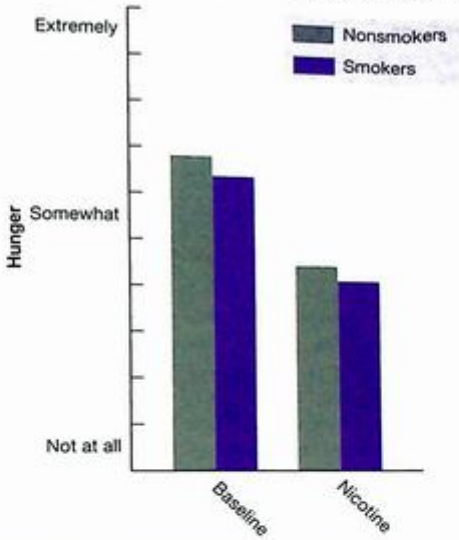
### Nicotine Affects Movement and Cognitive Functioning

Nicotine's behavioral effects include alterations in movement and cognitive function. These effects differ between naïve and chronic tobacco users. Nicotine produces effects on motor stability, which are particularly noticeable in the hands. Hand tremor and reduced hand steadiness occur after nicotine administration to non-tobacco users. Tolerance occurs with these effects in tobacco users (Perkins et al., 1994).

Nicotine's effects on psychomotor function also differ between acute and chronic administration. Acute administration of nicotine in nicotine-naïve users causes a decrease in psychomotor activity. However, sensitization to these effects occurs

**FIGURE 7.10 Appetite-Suppressing Effects of Nicotine**

After test subjects fasted overnight, administration of nicotine significantly reduced feelings of hunger in both smokers and nonsmokers compared to baseline (i.e., before nicotine administration).



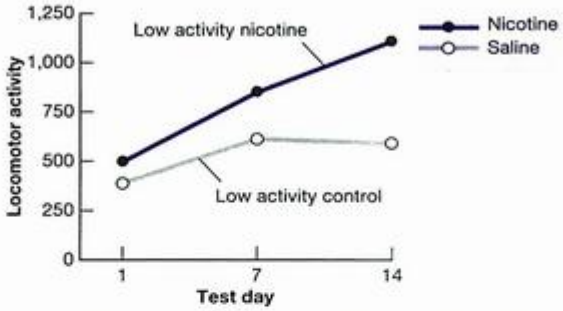

*Source:* Data from Perkins et al. (1991).

during chronic administration. Thus, in chronic tobacco users, nicotine increases psychomotor function. For example, Perkins and colleagues (1994) reported that nicotine administration increases the rate of finger tapping in chronic smokers, but decreases the rate of finger tapping in nonsmokers.

Animal studies also find differences between acute and chronic nicotine administration. For example, Pehrson and colleagues (2008) studied locomotor activity in rats during 14 days of nicotine administration using an open-field apparatus (**Figure 7.11**). An *open-field apparatus*, when used for rodents, consists of a box constructed from plastic or metal with walls high enough to prevent escape and an open top to allow for observation; open fields typically have grid lines drawn on the bottom. The grid lines allow researchers to count line crosses an animal makes as an index of overall movement. In place of grid lines, many open fields can emit photo beams instead; that is, researchers count photo beam breaks rather than line crosses. On the first day of treatment, nicotine suppressed locomotor activity as indicated by fewer photo beam breaks in an open-field apparatus. However, on the 7th and 14th days of treatment, nicotine enhanced locomotor activity.

**FIGURE 7.11 Behavioral Sensitization to Nicotine**

Nicotine-treated rats (solid symbols) exhibited increased locomotor activity on the 7th and 14th days of treatment compared to saline-treated rats. The *y*-axis shows locomotor activity as an expression of number of photo beams rats crossed within a test chamber. The *x*-axis refers to the number of days of treatment.




*Source:* Data from Pehrson et al. (2008).

Although public attitudes toward nicotine are generally negative, nicotine may show some benefits for cognitive functioning. Studies show that nicotine improves attention, particularly when reorienting attention toward another stimulus (Thiel, Zilles, & Fink, 2005), and improves information processing (Juliano, Fucito, & Harrell, 2011; Wesnes & Warburton, 1984).

In attention tasks, nicotine improves information processing by shortening times to detect stimuli. Wesnes and Warburton (1984) first demonstrated these effects, finding that nicotine improved the detection of targets during an 80-minute vigilance task consisting of identifying a number of sequences from numbers scrolling across a display. David Warburton later reflected that this seminal study was first rejected from a journal because the editor refused to publish "anything good about nicotine" (Warburton, 2002).

Nicotine's improvements in attention occur after chronic administration as well. For example, Perkins and colleagues (1994) used a *Stroop test*—a standard test of processing speed used for neuropsychological assessments that evaluates reaction times to mismatched stimulus presentations (Lansbergen & Kenemans, 2008)—to assess attention after nicotine administration in both nonsmokers and smokers. Nicotine improved reaction times in both test subjects, both nonsmokers and smokers.

Aside from information processing and attention, the effects of nicotine on memory are unclear. In the study by Perkins and colleagues (1994), nicotine also improved memory in a word list recall test, which required participants to remember words presented to them in a list. Nicotine's memory improvements were greater in nonsmokers than in smokers, suggesting that smokers develop a tolerance to these effects. Yet, many studies also fail to show improvements in memory after nicotine

treatment, and some studies show that nicotine worsens memory in chronic smokers (Ernst et al., 2001; Myers, Taylor, Moolchan, & Heishman, 2007; Park, Knopick, McGurk, & Meltzer, 2000).

## Nicotine's Positive and Negative Subjective Effects

Nicotine's subjective effects vary greatly between acute and chronic administration. In non-tobacco users, nicotine can produce negative subjective effects, including nausea and disequilibrium. In addition, as described in the study by Perkins and colleagues (1994), nicotine produces feelings of jitteriness, tension, and confusion in nonsmokers. Yet, acute tolerance to these negative subjective effects occurs after subsequent nicotine administrations. Further, many users instead feel relaxed after smoking for the first time. Researchers find a much greater risk of continued smoking for those feeling relaxed compared to those who experienced negative subjective effects (DiFranza et al., 2004).

A conditioned taste aversion procedure can demonstrate nicotine's aversive effects as well as acute tolerance to these aversive effects. The conditioned taste aversion procedure is described in **Box 7.1**. Prus and colleagues (2007) used this procedure to link the timing of nicotine administration with the time course of nicotinic-receptor changes (**Figure 7.12**). For rats treated with nicotine five minutes before a pairing session with saccharin, less saccharin was consumed on the following day. This pairing session took place during the activated nicotinic-receptor state.

# BOX 7.1

## CONDITIONED TASTE AVERSION

A *conditioned taste aversion* is the result of a pairing process between a noxious stimulus and a novel-tasting substance. This procedure also is called the *Garcia effect* in recognition of a discovery by John Garcia in 1955 (Garcia, Kimeldorf, & Koellino, 1955). Garcia discovered that rats ingested less of a saccharin solution after an occasion in which prior consumption of the solution was followed by gastrointestinal pain. Conditioned taste aversion is a process resembling classical, or Pavlovian, conditioning procedures.

Many psychoactive drugs function as noxious stimuli, allowing them to be studied in a conditioned taste aversion procedure. In a typical procedure, researchers give water-deprived rats access to two water bottles. One bottle contains the usual tap water, whereas the other bottle contains a novel, and often sweet-tasting, solution. After overcoming a *neophobic reaction*—that is, a rat's natural fear response to ingesting novel substances—rats consume the novel solution.

After a session in which rats consume the novel-tasting substance, researchers conduct one or multiple pairing sessions with a drug or its placebo. The timing of a drug injection is set to produce noxious effects after a session when subjects consume the novel substance. We refer to this type of session as a *pairing session*.

*(Continued)*

(Continued)

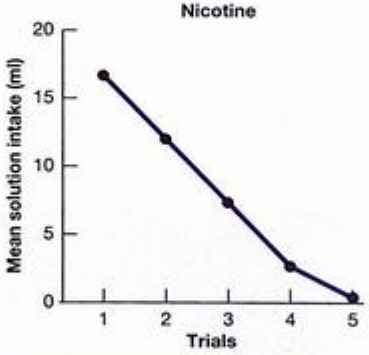
A conditioned taste aversion is demonstrated if significantly less solution is consumed during subsequent sessions.

For example, nicotine produces a robust conditioned taste aversion. In one of the earliest characterizations of nicotine in this procedure, Stolerman, Pratt, Garcha, Giardini, and Kumar (1983) conducted repeated pairings over several sessions with nicotine and a flavored solution consisting of either saccharin or sodium chloride. Selected results from this study are shown in **Box 7.1 Figure 1.** Over the course of several trials, the nicotine-paired solutions were consumed less, whereas saline-paired solutions were consumed at the normal level.

Although conditioned taste aversion appears to be only a measure of adverse effects, this is not necessarily the case. For many recreational drugs, the doses used to achieve positive subjective effects are the same doses effective for producing conditioned taste aversions (Wise, Yokel, & Wit, 1976).

**BOX 7.1 FIGURE 1 Conditioned Taste Aversion With Nicotine**

Less consumption of a flavored solution occurred after pairing the solution with the effects of nicotine in rats. The *x*-axis represents the number of consecutive pairing sessions, and the *y*-axis represents the volume of solution consumed.



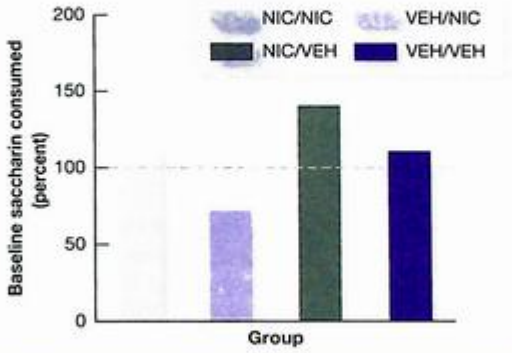

*Source:* Data adapted from Stolerman et al. (1983).

In this same study, another group of rats was treated with nicotine 90 minutes before the pairing session and given a second treatment of nicotine five minutes before the session. These rats drank more of the saccharin solution on the following day. For these rats, the second injection of nicotine occurred when the nicotinic receptors were desensitized, thus reducing aversive effects from occurring during or after the pairing session.

Long-term treatment with nicotine also causes tolerance to these negative subjective effects. Without negative subjective effects, chronic tobacco users experience only positive subjective effects from nicotine. In chronic smokers, nicotine

**FIGURE 7.12** **Acute Tolerance to Nicotine Using Conditioned Taste Aversion**

Nicotine failed to exhibit a conditioned taste aversion (NIC/NIC group) when it was administered during the nicotine receptor desensitized state. See text for further details.




*Source:* Prus, A. J., Maxwell, A. T., Baker, K. M., Rosecrans, J. A., & James, J. R. (2007). Acute behavioral tolerance to nicotine in the conditioned taste aversion paradigm. *Drug Development Research*, 68(8), 522–528. doi:10.1002/ddr.20219. Reproduced with permission of Wiley Inc.

administration produces feelings of vigor, arousal, and reduced fatigue (Perkins et al., 1994). Chronic smokers report that the effects of nicotine are pleasant and enjoyed and produce a positive mood (Myers et al., 2007). These smokers can detect a distinct rewarding effect with each puff of cigarette smoke.

The positive subjective effects of nicotine can be difficult to establish in animals. In a standard self-administration procedure (see Box 5.1), rats will not learn to self-administer nicotine because of the initial adverse effects experienced on first exposure to nicotine. In other words, if the effects are negative, an animal will avoid those effects rather than seek to achieve them. To observe the rewarding effects of nicotine in this procedure, researchers use a variation on the standard self-administration design.

For example, Boules and colleagues (2011) used a common design variation to study nicotine self-administration in rats. First, these researchers trained rats to press a lever for sucrose food pellets. Then, the researchers changed the consequence for pressing a lever from the sucrose food pellet to an intravenous nicotine injection. Because the rats had learned to repeatedly press the lever for sucrose pellets in the past, they persisted in pressing the lever, resulting in further nicotine injections. Through this process, tolerance quickly developed to nicotine's negative effects. After a tolerance developed to the negative effects, the rewarding effects of nicotine administration were sufficient to maintain lever pressing.

Other components in tobacco may contribute to the reinforcing effects of nicotine. In particular, MAO inhibitors found in tobacco enhance nicotine-induced effects on nucleus accumbens dopamine levels. Self-administration of nicotine is enhanced by MAO inhibition (Guillem et al., 2005; Villégier, Lotfipour, McQuown, Belluzzi, & Leslie, 2007). For example, in a study by Villégier and colleagues (2007), the MAO inhibitor tranylcypromine facilitated self-administration for nicotine in rats. This facilitation avoided the need to have a prior training history, allowing the researchers to use a standard self-administration procedure. Rats that did not receive the MAO inhibitor were unable to self-administer nicotine without altering the standard procedure. These findings suggest that an addiction to tobacco may develop more rapidly than an addiction to only nicotine.

## Adverse Effects of Tobacco Use

Many of the severely adverse effects associated with nicotine are the result of its vehicle: tobacco. Tobacco contains thousands of chemicals, including carcinogens such as nitrosamines. **Nitrosamines** are chemicals shown to produce cancerous tumor growth. The release and inhalation of tar from smoked tobacco provides direct contact of these carcinogens with tissue in the mouth, throat, esophagus, and lungs. E-liquids used for e-cigarettes tend to have low to no levels of nitrosamines (Pisinger & Døssing, 2014). Although safer in this regard, e-cigarette vapors include chemicals with potential to damage cells in the lungs, including aldehydes, which provide different flavorings for e-liquids, and formaldehyde, as noted earlier in the chapter (Pisinger & Døssing, 2014; Rowell & Tarran, 2015).

**Nitrosamines**
Chemicals shown to produce cancerous tumor growth

**Emphysema**
Type of chronic obstructive pulmonary disease caused by irreversible lung damage

Smoked tobacco is a cause of pulmonary diseases such as **emphysema**, a type of *chronic obstructive pulmonary disease* (typically abbreviated as COPD) caused by irreversible lung damage (**Figure 7.13**). The symptoms of emphysema include shortness of breath, wheezing, chronic cough, and fatigue. Emphysema patients are treated with a bronchodilator inhaler such as albuterol to open lung passages.

Tobacco use also increases the risk of cardiovascular disease. Nicotine in tobacco causes arteries and blood vessels to narrow and constrict, increasing heart rate. Together, these effects increase the risk of heart attack, stroke, and diseases associated with impoverished blood flow to other organs.

### Drug Profile: albuterol

| | |
|---|---|
| Brand name: | *Salbutamol* |
| Mechanism of action | $\beta_2$ adrenoceptor agonist |
| Uses | Addresses a poor ability to breathe common in disorders like asthma and COPD by dilating bronchi and bronchioles in the lungs (i.e., opening air passages) |

**FIGURE 7.13 Emphysema**

Emphysema, shown in the lung on the right, is a disease caused by smoking-related irreversible lung damage. A healthy lung is shown on the left.

*Healthy lung* *Emphysema*

Source: iStockphoto/ttsz.

During pregnancy, tobacco causes slower gestational development, preterm births, and low birth weight. Any number of chemicals in smoked tobacco can interfere with prenatal development, but reduced oxygen to the fetus is a significant contributor. Women who smoke also have an increased risk of breast cancer and may begin menopause at an earlier age than women who don't smoke (Perkins, 2001).

## Nicotine and Psychological Withdrawal

As noted earlier in this chapter, seven tobacco company CEOs famously testified that nicotine is non-addictive. This opinion, of course, lies in the best interest of tobacco companies, which seek to minimize tobacco regulation. Beyond this conflict of interest, the basis for their opinion depends on what particular addiction model one looks at.

As described in Chapter 5, traditional notions of drug addiction were largely based on opioids and alcohol. For drugs like these, addiction appears as an intense motivation to seek and use a substance, often at the expense of losing one's career or jeopardizing relationships with friends or family. We don't find this with nicotine use. When considering addiction from this specific viewpoint, the CEOs likely felt comfortable asserting the non-addictive nature of nicotine.

The American Psychiatric Association's *Diagnostic and Statistical Manual* (DSM-5), however, offers other features of *substance use disorders*; namely, that individuals express difficulty quitting or reducing use. When nicotine use discontinues, chronic users may experience a collection of psychological withdrawal symptoms called the **nicotine abstinence syndrome**, which is characterized by craving, irritability, anxiety, hostility, concentration difficulties, impatience, and insomnia. Avoidance of nicotine's withdrawal effects is an important contributor to tobacco usage. Based on the use disorder criteria described in the DSM, nicotine is an addictive substance. Further, as described previously in this chapter, nicotine exhibits a rapid tolerance to both physical and psychological effects during chronic use. Given our modern conceptions of substance use disorders, few people would agree with a tobacco company's claims that their products do not cause addiction.

**Nicotine abstinence syndrome**
Nicotine withdrawal symptoms characterized by craving, irritability, anxiety, hostility, concentration difficulties, impatience, and insomnia

E-cigarette use among those who have never used tobacco products garners concern for the development of a nicotine addiction. While few studies currently exist, a recent study by Vogel and colleagues (2019) might provide a clue. This study surveyed adolescent e-cigarette users concerning their frequency of e-cigarette use, finding that 14.5 percent used e-cigarettes on a daily basis while others used the products less frequently. The researchers came back to survey them again 12 months later. The survey results? The vast majority (80.3 percent) had continued using e-cigarettes, and among them, nearly a third (29.8 percent) used e-cigarettes on a daily basis. Moreover, 28.8 percent were now smoking cigarettes. In a different study, this time surveying younger adults (ages 18 to 24), regular e-cigarette users reported tolerance to the effects of e-cigarettes and a sense of loss of control over e-cigarette use (Chesaniuk, Sokolovsky, Ahluwalia, Jackson, & Mermelstein, 2019). Therefore, e-cigarette use might indeed facilitate a nicotine addiction and could lead to use of tobacco products, such as cigarettes.

## STOP & CHECK

1. During sustained use, nicotine produces a(n) _____ in locomotor activity.
2. Nicotine improves two particular aspects of attention: orientation to a stimulus and _____.
3. On first using nicotine, the positive subjective effects are overshadowed by _____ effects.
4. How might the reinforcing effects of tobacco differ in magnitude from the reinforcing effects of nicotine?

5. Many of the adverse effects associated with nicotine actually result from _____, the nicotine vehicle.

6. Repeated nicotine use causes an upregulation of nicotinic receptors, which is the result of _____ of nicotinic receptors.

1. increase. However, the first administration of nicotine causes a decrease in locomotor activity. The increase in locomotor activity during sustained nicotine use is described as sensitization. 2. information processing 3. aversive 4. Tobacco smoke contains many chemicals that may enhance nicotine's reinforcing effects. Therefore, smoking may produce a greater reinforcing effect than nicotine alone. 5. tobacco 6. desensitization

## Environmental, Genetic, and Receptor Differences Between Light and Heavy Tobacco Users

Humans vary in their susceptibility to nicotine addiction. People who are the most resistant to nicotine addiction are called *chippers*. These are regular, but generally nondaily, smokers who fail to develop an addiction to tobacco. **Chippers** are long-term smokers, but they typically smoke only up to a few cigarettes a day and again may not smoke on a daily basis. They make up approximately one-third of all smokers (Shiffman, 1989). The term *chipper* can also be applied, as a nontechnical term, to any occasional user of abused drugs.

**Chippers**
Smokers who fail to develop an addiction to tobacco

Chippers smoke cigarettes the same way as normal smokers—that is, they fully inhale tobacco smoke, have the same puff duration, and have the same interval times between puffs (Brauer, Hatsukami, Hanson, & Shiffman, 1996). Chippers and regular smokers have similar abilities to absorb and metabolize nicotine. However, chippers fail to show significant pharmacological effects from tobacco, and they fail to exhibit withdrawal symptoms when deprived of tobacco.

Exactly how chippers resist nicotine addiction is unknown. Two possible explanations concern environmental and genetic factors. For an environmental explanation, Shiffman (1989) found that chippers, more often than smokers, had greater coping skills, less stress, and better social support structures. These psychosocial factors may reduce an individual's risk of developing a substance addiction.

Genetically, chippers and chronic smokers differ in gene expression for $\alpha_5$, $\alpha_3$, and $\beta_4$ receptor subunits, which are found on chromosome 15 (Saccone et al., 2007). Of these, the single nucleotide polymorphism Chrna4 for the $\alpha_5$ unit is particularly associated with greater risk of nicotine dependence. Although this subunit has not been directly implicated in the reinforcing effects of nicotine, this subunit alters state changes from active to desensitized in $\alpha_4$ subunit-containing nicotinic receptors (Ramirez-Latorre et al., 1996). As noted already in this chapter, $\alpha_4\beta_2$ receptors facilitate the rewarding effects of nicotine.

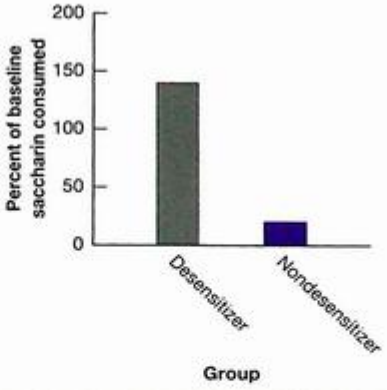
These genetic variations suggest that differences in nicotinic receptors may facilitate the resistance of chippers for nicotine addiction. In particular, chippers may have weaker acute tolerance to the effects of nicotine because of diminished

desensitization of nicotinic receptors. Reduced acute tolerance to nicotine would produce longer-lasting effects (Rosecrans, 1995).

To better understand nicotine tolerance in chippers, animal studies have assessed the association between nicotinic receptor desensitization and acute tolerance. For example, rats that differed in nicotinic receptor desensitization were studied in the conditioned taste aversion procedure study by Prus and colleagues (2007) described previously. As in the earlier experiment, rats were injected with nicotine both 90 minutes and five minutes before a pairing session. The rats used for this experiment were either normal or had diminished nicotinic receptor desensitization. In the normal rats, saccharin consumption increased the following day because the injection of nicotine five minutes before the pairing session occurred during the nicotine receptors' desensitized state, preventing aversive effects. However, in the rats with diminished nicotinic receptor desensitization, saccharin consumption decreased the following day because the receptors were not desensitized and thus did not prevent aversive effects (**Figure 7.14**). These data suggest that differences in nicotinic receptor desensitization differ between individuals and that these differences significantly alter acute tolerance to nicotine.

**FIGURE 7.14** **Conditioned Taste Aversion for Nicotine in Rats Exhibiting Low Nicotinic Receptor Desensitization**

Nicotine administered during the desensitized nicotinic-receptor state produces a conditioned taste aversion in rats that exhibit reduced nicotinic-receptor desensitization. See text for further details.




Source: Prus, A. J., Maxwell, A. T., Baker, K. M., Rosecrans, J. A., & James, J. R. (2007). Acute behavioral tolerance to nicotine in the conditioned taste aversion paradigm. *Drug Development Research*, 68(8), 522–528. doi:10.1002/ddr.20219. Reproduced with permission of Wiley Inc.

## STOP & CHECK

1. Chippers smoke without developing a nicotine addiction, possibly because they exhibit weaker _____ tolerance to nicotine.
2. Which subunit of the nicotinic receptor appears most related to reduced sensitization of nicotinic receptors?

1. acute 2. the $\alpha_5$ subunit

## From Actions to Effects: Why People Smoke and How They Quit

Humans learn to use tobacco for many reasons. Many people begin smoking because their friends smoke. Smoking may also be common in an individual's family or culture. Tobacco advertisers market cigarettes as fun, cool, sexy, and rebellious. Not too long ago, workers who smoked were allowed frequent short smoke breaks, whereas nonsmokers had to continue working.

As smoking persists, an addiction to nicotine develops, serving as the primary reason for tobacco use. For frequent smokers, the effects of nicotine become associated with routine, everyday activities such being on a smartphone or watching TV. Associative learning processes incentivize these conditioned responses, leading to the preoccupation and anticipation features of addiction as described in Chapter 5. Without having a cigarette, these stimuli lead to craving tobacco, which makes quitting difficult.

Many people succeed in quitting tobacco "cold turkey," while others need to participate in a treatment plan. Many psychotherapeutic approaches address the behavioral cues that trigger a craving to smoke. Smokers learn to identify the causes of these cravings and make attempts to diminish the influence of these cravings. No matter the method, studies generally show that reaching two weeks of tobacco abstinence most strongly predicts long-term success.

Looking into the two-week success correlation, Lussier and colleagues (2005) examined smokers using choice comparisons between desire to smoke versus earning small amounts of money among those who successfully or unsuccessfully abstained from smoking after two weeks. They found that far fewer of the abstinent smokers selected a desire to smoke over an option to earn money when given the choice. However, those still smoking after two weeks more often selected the desire to smoke option. Thus, the rewarding value of tobacco appears to weaken after reaching two weeks of tobacco abstinence. We also learn that two weeks of tobacco abstinence leads to less craving when exposed to stimuli associated with former tobacco use (Bradstreet et al., 2014).

Many treatment plans also employ pharmacological strategies in order to address the absence of nicotine in the body. As described previously, nicotinic receptors are upregulated during chronic nicotine administration, creating a need for nicotine to maintain this sensitized state. An abrupt drop in nicotine levels leaves these extra receptors inactivated, leading to withdrawal symptoms. Therefore, pharmacological treatments mostly fall into one of three categories: nicotine replacement therapy, nicotinic-receptor agonism, and antidepressant drugs (Polosa & Benowitz, 2011).

**Nicotine replacement therapy**
Therapy that consists of using a nontobacco nicotine product to minimize symptoms

**Nicotine replacement therapy** consists of using a non-tobacco nicotine product to minimize or prevent withdrawal symptoms. Nicotine replacement therapy products include nicotine skin patches, gum, nasal spray, and inhalers. To reduce their dependence on nicotine, users gradually reduce the dose of nicotine used until they reach a point where few withdrawal symptoms occur in the absence of nicotine. This approach may take weeks to several months.

Yet even with regard to use of nicotine replacement products, studies show that long-term smoking success relies on complete cessation of smoking. Kenford and colleagues (1994) evaluated smoking abstinence success among participants using a nicotine patch. In one of their experiments, they found that the 41 percent who were not smoking after two weeks from using the patch were still abstinent at a six-month follow-up. These findings contrast dramatically with those using a patch but still smoking after two weeks using the patch: at a six-month follow-up, 97 percent were still smoking. These and subsequent studies reveal that reaching two weeks of tobacco abstinence strongly predicts long-term success.

Nicotinic-receptor agonist medications also reduce withdrawal symptoms. The first drug from this class approved by the Food and Drug Administration is *varenicline* (*Chantix*), a partial agonist for nicotinic receptors (Coe et al., 2005). By acting as a partial agonist, less activation of nicotinic receptors occurs compared to a full agonist like nicotine. Varenicline also binds to the nicotine receptors that nicotine would normally bind to, preventing nicotine's effects. This may reduce the amount of dopamine released compared to nicotine, but some dopamine release also serves to substitute for nicotine's effects, which may help with nicotine withdrawal. When varenicline is taken, users report that smoking becomes less enjoyable and overall produces weaker effects (Gonzales et al., 2006; Polosa & Benowitz, 2011). However, these pharmacological actions tend to reduce smoking in fewer than half of all smokers (Gonzales et al., 2006).

## Drug Profile: varenicline

| | |
|---|---|
| Brand name | *Chantix* |
| Mechanism of action | Partial agonist for nicotinic receptors |
| Uses | Reduces withdrawal symptoms from nicotine dependence |

Antidepressant drugs reduce smoking by addressing nicotine's effects on dopamine by acting as dopamine reuptake inhibitors. The most commonly prescribed antidepressant drug for nicotine cessation is *bupropion* (*Zyban* or *Wellbutrin*). By blocking reuptake of dopamine, bupropion elevates dopamine levels within synapses. Researchers hypothesize that when this occurs in the nucleus accumbens, the elevated dopamine levels compensate for dopamine elevations normally produced by nicotine. Although this drug produces pharmacological actions suggestive of reducing smoking, fewer than one-third of patients in clinical studies have successfully abstained from smoking when taking bupropion (Gonzales et al., 2006).

## Drug Profile: bupropion

| | |
|---|---|
| Brand name | *Zyban* or *Wellbutrin* |
| Mechanism of action | Blocks reuptake of dopamine |
| Uses | Reduces withdrawal symptoms from nicotine dependence by substituting for nicotine's rewarding effects |

No matter the cessation treatment, rates of successful abstinence remain poor overall. There appear to be trends depending on gender, race, and socioeconomic status. In one study, Piper and colleagues (2010) evaluated 2,850 smokers enrolled in different types of cessation trials, including nicotine replacement therapies, bupropion, or a combination of bupropion and a nicotine replacement strategy. The smokers group consisted of men and women of either African or European American descent as well as different levels of socioeconomic status. After six months, the researchers found greater abstinence among men (vs. women), European Americans (vs. African Americans), and those with higher socioeconomic status (vs. low socioeconomic status). A combination of bupropion with a nicotine replacement product was most effective in men, whereas none of the therapies appeared ideal for African Americans. No matter the demographic characteristics or therapy used, none of the groups achieved greater than approximately 50 percent smoking abstinence at a six-month follow-up.

In another examination of sex differences in smoking, Cosgrove and colleagues (2012) examined sex steroid hormone levels and used single-photon emission computed tomography (typically abbreviated as SPECT) to examine $\beta_2$-containing nicotinic-receptor levels in smoking and nonsmoking men and women. They found that men who smoke express upregulation of $\beta_2$ nicotinic receptors compared to men who do not smoke, while no upregulation was observed in women who smoke. Further, during the luteal phase when progesterone levels are high, women who smoked expressed greater cravings to smoke and more symptoms of nicotine withdrawal compared to the follicular phase, when estradiol slowly rises from low

levels during the phase and progesterone levels are low. These findings might suggest why nicotine replacement products appear less effective in women (i.e., no change in $\beta_2$ nicotinic-receptor levels) and why women appear less susceptible to smoking relapse if therapy begins during the luteal phase of the menstrual cycle (Allen, Allen, Lunos, & Hatsukami, 2009). Overall, there remains much to learn about tobacco addiction and a great need for improved treatment approaches.

## STOP & CHECK

1. Given that the first use of nicotine causes aversive effects, why does tobacco use continue?
2. Why are nicotine replacement therapies helpful for tobacco cessation programs?

1. Behavioral reasons account for the persistent use of tobacco until tolerance to adverse effects develops. 2. Nicotine replacement therapies address changes that chronic nicotine use causes to the nicotinic-receptor system. A nicotine replacement therapy provides a gradual reduction in physiological nicotine levels, allowing this receptor system to slowly adapt to a nicotine-free state, thereby reducing withdrawal symptoms.

## Caffeine

**Caffeine**
Psychostimulant compound and a member of the xanthine chemical class

**Caffeine** is a psychostimulant compound and a member of the xanthine chemical class. Other xanthines, including theobromine and theophylline, also exhibit psychostimulant effects. Caffeine is by far the most used. Approximately 90 percent of Americans consume caffeine on a regular basis and average about 227 milligrams (mg) of caffeine per person each day (Frary, Johnson, & Wang, 2005). Best estimates indicate that children consume about half the caffeine as adults, although data on young children are generally lacking (Temple, 2009). In one study, average caffeine intake consisted of 52 mg in 5- to 7-year-olds and 109 mg in 8- to 12-year-olds (Warzak, Evans, Floress, Gross, & Stoolman, 2011).

### Caffeine and Related Compounds in Plants

Caffeine, and to a lesser extent other xanthine compounds, exist in many plants grown naturally in the environment. Caffeine, theobromine, and theophylline are found in kola nuts and cocoa tree nuts, which we use for cola soft drinks and chocolate, respectively. Colas contain caffeine from kola nuts, and chocolate has caffeine from cocoa nuts. A large variety of tea leaves also contain caffeine, theobromine, and theophylline. Coffee beans, which are brewed for coffee drinks, are a significant source of caffeine. Because caffeine represents the most-used and strongest-acting compound among naturally occurring xanthines, this section of the chapter focuses on the use and properties of caffeine.

The caffeine content among products varies. A 10-ounce (oz.) cup of regular coffee contains approximately 200 mg of caffeine, and a 16-oz. coffee contains

approximately 320 mg of caffeine. For coffee, the caffeine content varies, in part, with roasting time. Darker roast coffees, which are roasted longer, tend to have less caffeine content than lighter roast coffees.

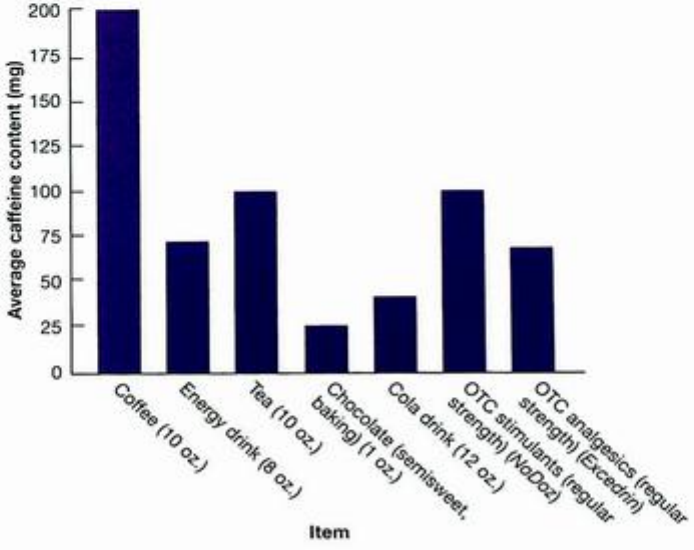
A 10-oz. cup of tea contains approximately 100 mg of caffeine, or half as much caffeine as coffee. A 1-oz. piece of chocolate contains approximately 25 mg of caffeine. **Figure 7.15** lists the caffeine content of other popular substances.

Energy drinks rapidly grew in popularity because of their invigorating properties. They contain a large amount of caffeine, often around 200 mg. Beyond describing energy-enhancing effects, advertisers also promote energy drinks for weight loss, physical stamina, and athletic performance. Individuals 25 years and younger, including a significant portion of children 12 and younger, consume nearly half of all energy drinks. College students report that between 39 percent and 57 percent had consumed energy drinks within the previous month (Malinauskas, Aeby, Overton, Carpenter-Aeby, & Barber-Heidal, 2007; Miller, 2008).

Energy drinks include not only caffeine as a direct ingredient but also may include caffeinated products such as kola nut, yerba maté, and cocoa. They often include other xanthines such as theobromine and theophylline. Many other chemicals

**FIGURE 7.15 Caffeine Content**

Caffeine content in selected beverages, foods, and medicines. OTC stands for "over the counter."




*Source:* Mayo Foundation (2011); Reissig et al. (2009).

in energy drinks, including sugar and a variety of herbs, amino acids, and plant extracts, promote energy-enhancing effects (Arria & O'Brien, 2011).

Alcoholic beverages have become a source of caffeine. These beverages, referred to as **caffeinated alcoholic beverages**, consist of mixing energy drinks such as Red Bull with alcohols such as vodka. The energy drink component of these beverages can temporarily counter alcohol's intoxicating effects, thus facilitating excessive drinking and an increased risk of alcohol poisoning.

**Caffeinated alcoholic beverage**
Beverage made by mixing energy drinks with alcohol

## Caffeine Has an Ancient History

The plant products just listed were consumed long before the Europeans discovered them. Teas were used in China for thousands of years, and coffee beans were brewed in Arabia since at least A.D. 1000. In South and Central America, the Olmec, Maya, Toltec, and Aztec cultures consumed cocoa beans. European explorers subsequently brought cocoa seeds to Europe, and Europeans harvested the seeds and commonly prepared cocoa with sugars and milk to make chocolate drinks and candies.

The very first human discoveries of the invigorating properties of these plants are shrouded in stories passed through an oral history, as reviewed by Fredholm (2011). For example, scholars often report a story about an Ethiopian named Kaldi as the discoverer of coffee. Kaldi observed that his goats became excited after consuming berries from a coffee bush, which he confirmed on trying the berries himself.

Before A.D. 1000, people normally consumed coffee by eating coffee beans, but around A.D. 1000, brewed coffee became popular. Brewed coffee became a social drink in Arabia, and students and scholars consumed coffee in intellectual centers. In fact, a type of coffee bar consumed in intellectual centers in Turkey was given the name *mekteb-i-irfan*, meaning "the school of the wise."

Coffee was not immediately accepted in Europe, and an attempt to persuade Pope Clement VIII (reign 1592 to 1605) to officially ban this "Muslim drink" led him to state, "This satanic drink is in truth so good that it would be a pity if only nonbelievers were allowed to drink it. We will fool Satan and baptize it so that it becomes a Christian drink, with no danger for the soul" (Fredholm, 2011). Thus, any social barriers to coffee consumption in Europe soon fell.

The first European cafés appeared in the early 1700s. These cafés were male-only establishments that not only served coffee but also sold newspapers and cultural reviews. The British, however, preferred tea, possibly because of the influence of the British East India Company, which facilitated a strong tea trade with India. Russia also preferred tea over coffee, possibly because of that nation's ties with China.

Friedlieb Runge first extracted caffeine in 1819, and Emil Fischer identified caffeine's chemical properties in 1881. Other xanthine discoveries came later. Theobromine was first extracted in 1841, and Fischer discovered its chemical structures in 1882. Soon after this, Fischer discovered theophylline, another xanthine.

## STOP & CHECK

1. In addition to coffee, teas, and soda, energy drinks are a major source of _____.
2. Coffee beans have been brewed since at least A.D. 1000 in _____.

1. caffeine 2. Arabia

## Caffeine Absorption, Duration, and Interaction With Other Psychoactive Drugs

Caffeine products are administered orally in the form of beverages, food, or pills. Coffee contains a number of acids, called *chlorogenic acids*, that lower the pH of coffee to generally between five and six, with caffeine itself a weak base (Fujioka & Shibamoto, 2008). Once ingested, 100 percent of caffeine is absorbed through intestinal walls, reaching peak blood levels after approximately 40 minutes (Blanchard & Sawers, 1983; Liguori, Hughes, & Grass, 1997). Caffeine penetrates both brain and placental blood barriers. The liver metabolizes caffeine primarily by the enzyme CYP-1A2 and, to a lesser extent, by the enzyme CYP-2E1. Most individuals metabolize approximately 90 percent of caffeine, although the amount of caffeine metabolized depends on the activity of these enzymes. For example, individuals with reduced CYP-1A2 enzymatic activity metabolize less caffeine, subsequently prolonging caffeine's pharmacological effects.

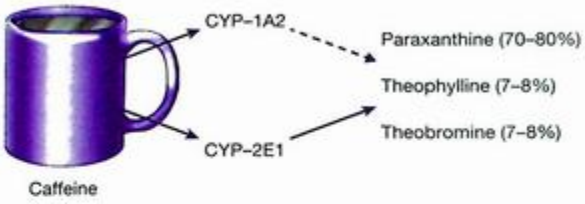
Enzymatic involvement with other drugs also may alter the metabolism rate for caffeine. For example, many antidepressant drugs are CYP-1A2 enzyme inhibitors. Thus, individuals who take these antidepressant drugs metabolize less caffeine. Given that caffeine can produce anxiousness (see "Pharmacological Effects" later in the chapter), this interaction effect may weaken an antidepressant drug's effectiveness if caffeine intake is not monitored (Fredholm & Arnaud, 2011). At the same time, smoking enhances CYP-1A2 activity, resulting in increased metabolism of caffeine (Begas, Kouvaras, Tsakalof, Papakosta, & Asprodini, 2007; Joeres et al., 1988).

The metabolism of caffeine produces active metabolites that, like caffeine, belong to the xanthine class of drugs (**Figure 7.16**). In particular, these metabolites include theophylline, theobromine, and another xanthine compound with related psychoactive effects, paraxanthine. Unlike theophylline and theobromine—which, as stated earlier, occur naturally in plants—paraxanthine occurs only when metabolically converted from caffeine. The relative distribution of metabolites produced from caffeine consists of 70–80 percent paraxanthine, 7–8 percent theophylline, and 7–8 percent theobromine (Begas et al., 2007).

The body primarily eliminates caffeine through the kidneys. The rate of elimination varies widely from approximately 3 to 10 hours (Blanchard & Sawers, 1983). The range in elimination rates may explain why some individuals have difficulty

**FIGURE 7.16 Caffeine Metabolites**

The liver enzymes CYP-1A2 and CYP-2E1 convert caffeine into xanthine metabolites, including theophylline and theobromine. The dashed arrow indicates that less conversion occurs from CYP-1A2 to theophylline and theobromine.




sleeping at night if they drink coffee in the afternoon, whereas other individuals have no difficulty sleeping at night even after drinking coffee in the evening. Cigar or cigarette smoking doubles the rate of caffeine elimination because of the previously mentioned increased metabolic activity (Joeres et al., 1988). Because of this increased elimination rate, smokers may drink more coffee to maintain caffeine's effects.

## Caffeine: Antagonist for Adenosine Receptors

**Adenosine**
A neuromodulator that has inhibitory effects on neurons throughout the central and peripheral nervous system

Caffeine's primary mechanism of action is antagonism of adenosine A1 and A2 receptors. **Adenosine** is a neuromodulator that has inhibitory effects on neurons throughout the central and peripheral nervous system. In particular, adenosine has inhibitory effects on cholinergic neurons in the cerebral cortex and on dopamine neurons in the basal ganglia. Through these actions, we know adenosine as a chemical that contributes to sleepiness. By blocking adenosine receptors, caffeine prevents the inhibitory influence of adenosine within these parts of the brain, thus promoting alertness (Fisone, Borgkvist, & Usiello, 2004).

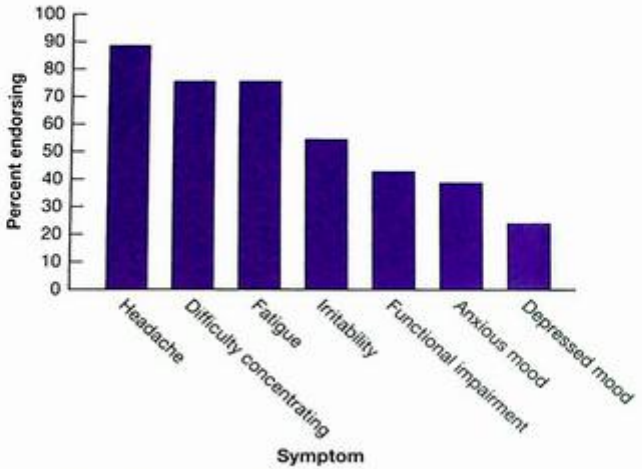
## STOP & CHECK

1. How can enzymatic activity in the liver influence caffeine's effects?
2. Caffeine is an antagonist for _____ receptors.

1. The behavioral effects of caffeine will persist longer in individuals who are slower metabolizers of caffeine. In a slow metabolizer, caffeine's effects may persist into nighttime and interfere with sleep. In addition, drugs may interact with CYP-1A2 enzymes, potentially slowing the metabolism of caffeine.
2. adenosine

**FIGURE 7.17 Caffeine Withdrawal Symptoms**

Many study respondents who reported a desire to reduce and quit caffeine reported withdrawal symptoms.




*Source:* Data from Juliano et al. (2012).

## STOP & CHECK

1. An increase in positive mood is one of the many _____ effects of caffeine.
2. Excessive doses of caffeine can produce _____, which is characterized by agitation, anxiety, insomnia, and other symptoms.
3. Other chemicals in energy drinks may interact with _____ drugs, causing an increase in adverse effects.
4. In the absence of caffeine, hostility, fatigue, and negative mood are indications of _____ on caffeine.

1. psychostimulant 2. caffeinism 3. antidepressant 4. dependence

## From Actions to Effects: Caffeine Habit?

Improvements in mood and alertness are common reasons for seeking caffeinated products such as coffee, tea, and other caffeinated beverages. Moreover, these and other products, such as chocolate, taste good, which adds to their appeal. Yet during

the course of repeated use, a dependence on caffeine, as indicated by withdrawal symptoms, may facilitate consumption of caffeinated products.

Given the prevalence of caffeine use, most readers of this text probably consume caffeinated products on a daily basis. In particular, you may use coffee, a soft drink, or an energy drink to help wake up in the morning. If this describes you, then consider this: Is the tiredness you feel in the morning natural—or is it caffeine withdrawal?

Assuming that you do not consume a caffeinated product within several hours before bedtime, sleeping six to eight hours may provide for a total caffeine abstinence period of about 10–12 hours. This abstinence period exceeds caffeine's elimination half-life, suggesting that your body's caffeine levels will be low or absent by morning. Indeed, many studies describe morning as an early withdrawal state for chronic caffeine users (James & Rogers, 2005). Thus, for most people, caffeine's ability to fight morning sleepiness may have a lot to do with removing caffeine's withdrawal symptoms.

The DSM-5 considers *caffeine intoxication*, generally similar to caffeinism presented earlier, and *caffeine withdrawal* as two potential disruptive features of caffeine use. Although the DSM-5 does not consider caffeine as generating a specific substance use disorder, some clinical studies characterized problem caffeine use as meeting the general features of a disorder (Bernstein, Carroll, Thuras, Cosgrove, & Roth, 2002; Griffiths & Chausmer, 2000). In an assessment of caffeine dependence, Bernstein and colleagues (2002) evaluated caffeine use among a sample of U.S. teenagers. Among the 36 teenagers assessed, 22.2 percent exhibited a sufficient number of symptoms to meet the DSM diagnostic criteria for a substance use disorder. The most commonly observed symptoms included tolerance, withdrawal symptoms, desire to quit or unsuccessful efforts to control use, and continued use despite physical or psychological problems. The total group of teenagers studied reported 244 mg of caffeine per day, with values ranging from as little as 49 mg to as much as 767 mg of caffeine per day.

Although some researchers support applying substance use disorder criteria to caffeine use, others are unconvinced. In a review of scientific studies that assessed caffeine use, Satel (2006) concluded that caffeine does not meet substance dependence criteria. Key points in Satel's study consist of weak or inconsistent reporting of withdrawal effects and a failure to demonstrate strong compulsions to use caffeine. Given that caffeine appears neither irresistible nor a cause of social disruption, Satel argues that caffeine fails a commonsense test as an addictive substance.

## CHAPTER SUMMARY

This chapter has covered two widely used psychostimulant drugs: nicotine and caffeine. Tobacco products are the key source of nicotine. Cigarette smoking is the most common form of nicotine administration, but other forms of tobacco such as smokeless tobacco and e-cigarettes are popular as well. Tobacco use has a long history, dating back to the ancient uses in the Americas and then reaching

Europe after Columbus's expedition to the New World.

Nicotine is delivered to the body from tobacco or e-liquids and is absorbed through tissues in the lungs, throat, mouth, and skin. Inhalation is the most efficient route for nicotine delivery. Nicotine is metabolized in the liver, producing cotinine, an active metabolite.

Nicotine produces an increase in nucleus accumbens dopamine levels by activating nicotinic cholinergic receptors in the nucleus accumbens and ventral tegmental area. Cotinine also is an agonist for these receptors, but it has a much weaker affinity than nicotine. Nicotine increases sympathetic nervous activity and increases locomotor activity during repeated administration. Nicotine also improves attention. Subjectively, nicotine produces adverse effects on first usage, but tolerance to the effects soon subsides to reveal positive subjective effects. Most of nicotine's adverse effects are the result of tobacco, which contains many known cancer-causing agents. In addition to cancer, tobacco increases the risk of cardiovascular disease and lung disease. Because of desensitization at nicotinic receptors, upregulation of nicotinic receptors occurs during chronic use. Upregulation leads to a sensitized behavioral state.

Nicotine addiction accounts for chronic, habitual tobacco use. Quitting nicotine is difficult in part because of the association of tobacco use with everyday activities. Further, upregulation of nicotinic receptors facilitates a physiological dependent state, requiring sustained elevated nicotine levels for normal functioning.

Caffeine is a xanthine psychostimulant drug found naturally in kola nuts, cocoa tree nuts, and tea leaves. The most common caffeine sources include coffee, tea, and energy drinks. Caffeine-containing leaves and nuts were long used in China and Arabia, and teas and coffee were used throughout Europe beginning in the 1700s.

Caffeine is orally administered and is metabolized in the liver. Caffeine's elimination rate varies, depending on liver enzymatic activity. Caffeine's effects are derived through antagonism of adenosine receptors, producing not only an improvement in alertness, mood, and energy, but also a facilitation of dopamine's effects on the sympathetic nervous system. Excessive caffeine intake produces caffeinism, which is characterized by agitation, anxiety, and negative mood. Tolerance soon develops to caffeine's effects during chronic use, and continued caffeine use is mostly maintained by avoidance of caffeine withdrawal symptoms.

## KEY TERMS

Nicotine 204
Cigarette 205
Cigar 205
Hookah 205
Smokeless tobacco 205
E-cigarettes (or electronic nicotine delivery systems) 205
Vaping 207
Secondhand smoke 209
Thirdhand smoke 209
Flue curing 212
Tar 213
Cotinine 214
Functional antagonism 215
Upregulation 217
Acute tolerance 220
Nitrosamines 226
Emphysema 226
Nicotine abstinence syndrome 228
Chippers 229
Nicotine replacement therapy 232
Caffeine 234
Caffeinated alcoholic beverages 236
Adenosine 238
Caffeinism 239

CHAPTER 8

# Depressants

## Chapter Outline

- Types of Depressant Substances
- Depressants and GABA Neurotransmission
- Barbiturates
- Benzodiazepines
- Z-Drugs
- Gamma-Hydroxybutyrate (GHB)
- Inhalants
- From Actions to Effects: Stimulus Properties of GHB and Toluene

## Learning Objectives

- Discuss the characteristics of depressant substances
- Examine GABA's role in the effects of depressant substances
- Interpret the pharmacokinetic actions of depressants in the context of their manner and reasons for use
- Evaluate the effects of depressants and relate these effects to the pharmacological actions of these drugs

Chapters 6 and 7 dealt with psychostimulants—substances that stimulate activity. For Chapter 8, we shift to the opposite direction by reviewing substances that diminish activity. Chapter 8 provides an overview of depressant substances and presents barbiturates, benzodiazepines, GHB, and agents administered in vaporous form called *inhalants*. The most widely consumed depressant substance—alcohol—

gets its own chapter (Chapter 9), as do opioids (Chapter 10) and cannabinoids (Chapter 11).

## Types of Depressant Substances

**Depressant**
A drug or substance that diminishes physiological activity and cortical arousal

A **depressant** drug diminishes physiological activity and cortical arousal. Depressants commonly exhibit positive subjective effects, facilitating recreational use and abuse of these substances. However, the effects profile of depressant substances depends upon the manner of use. Recreational users seeking depressants for their positive subjective effects tend to experience a far greater degree of mood-elevating effects compared to those using these substances instrumentally, such as for reducing anxiety. The most commonly consumed depressant substance is alcohol, and others include barbiturates, benzodiazepines, opioids, and cannabinoids. We refer to these substances as depressants because exhibiting depressant effects is a primary feature of their overall effects.

The prevalence of depressant use leads to a number of commonly used terms that tend to reflect the calming effects of these substances. One of these terms is a *sedative*, a direct reference to the sedating (i.e., calming) effects of a drug. Another is a *tranquilizer*, many times preceded with *major* or *minor* as a way of referring to the potency of the drug's effects.

An older term, and one that you'll find in mid-20th century Western literature, is a *bromide*. The term comes from the effectiveness, albeit modest compared to modern drugs, of certain compounds with bromine that were effective as sedatives and for inhibiting convulsions in epilepsy. Medicinal forms of bromine included potassium bromide or sodium bromide, which were used starting around the 1850s (Balme, 1976). Bromide compounds became associated with progressively increasing adverse effects during use and incidents of psychotic symptoms, which limited their use as alternative compounds became available in the early and mid-1900s.

## Depressants and GABA Neurotransmission

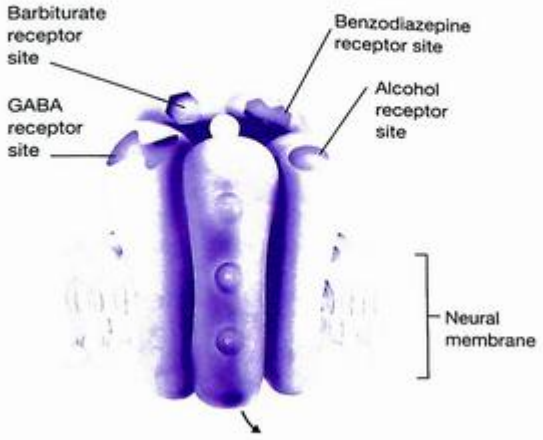
Neurologically, most central nervous system depressant drugs act directly or indirectly via the brain's most common inhibitory neurotransmitter, GABA. As noted in Chapter 4, drugs can alter neurotransmission through a variety of ways. For barbiturates, benzodiazepines, inhalants, and alcohol, depressant effects occur via their direct actions on the $GABA_A$ receptor. We find $GABA_A$ receptors in brain structures that appear linked to a drug's depressant effects, including the cerebral cortex, thalamus, hippocampus, cerebellum, and the basal ganglia (Wisden, Laurie, Monyer, & Seeburg, 1992). For other substances, depressants might increase the activity of GABA neurons.

**$GABA_A$ receptor**
Ionotropic receptor composed of five subunits and activated by the neurotransmitter GABA

The **$GABA_A$** receptor consists of an ionotropic receptor formed by five subunits that allows entry of the negatively charged ion chloride ($Cl^-$) into neurons (**Figure 8.1**). Inflow of $Cl^-$ diminishes the activity of neurons, decreasing the neuron's firing rate of action potentials. Of the five subunits that make up the $GABA_A$ receptor, two are of the $\alpha$ type and two are of the $\beta$ type. The fifth is a bit of a

**FIGURE 8.1 The $GABA_A$ Receptor**

The $GABA_A$ receptor is an ionotropic receptor with a neurotransmitter site for GABA, in addition to many allosteric sites. A number of depressant drugs exert pharmacological actions through binding to allosteric sites on the $GABA_A$ receptor.




wild card: It can be a γ, ρ, δ, or ε subunit. In addition to the several types of $GABA_A$ receptor subunits, each subunit has multiple subtypes. Six subtypes of the α subunit, four subtypes of the β subunit, and six subunits of the γ subunit are currently known. We identify these different subtypes using subscript numbers, such as $\alpha_2$ or $\beta_3$. The complex has binding sites for GABA, barbiturates, benzodiazepines, and alcohol.

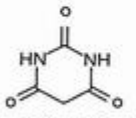
The $GABA_A$ receptor provides two binding sites for the neurotransmitter GABA. These sites exist in regions formed where an α subunit joins a β subunit. GABA must occupy both sites to open the $GABA_A$ receptor. Beyond having a site for the neurotransmitter GABA, the receptor protein hosts a number of allosteric sites that affect the receptor's activity. Many depressant drugs act through allosteric sites on the $GABA_A$ receptor to facilitate GABA neurotransmission. In fact, many of the sites have been named after the drug classes that specifically bind to them. The receptor shown in Figure 8.1 identifies an allosteric site for barbiturate, benzodiazepine, and beverage alcohol (referred to as the ethanol site).

## Barbiturates

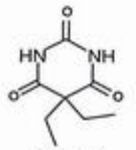
Sedative barbiturate drugs became available in the early 1900s after German chemists Emil Fischer and Josef von Mering developed barbital (**Figure 8.2**) (Fischer & von Mering, 1903; Shorter, 1997). Barbital was synthesized as a derivative of an

**FIGURE 8.2 Chemical Structures for Selected Barbiturate Compounds**

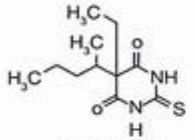
The class of psychoactive barbiturate drugs was derived from the compound barbituric acid. Note the features of barbituric acid in the structures of psychoactive barbiturate drugs in the barbiturate drugs sampled in this figure.



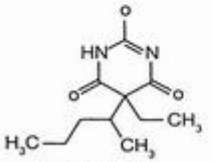

**Barbituric Acid**



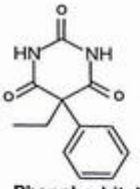

**Barbital**




**Thiopental**




**Pentobarbital**




**Phenobarbital**

earlier compound, barbituric acid, discovered years earlier by Adolf von Baeyer, who may have named it after his girlfriend, Barbara. The Bayer company—named after Friedrich Bayer—produced barbital under the name *Veronal* for medicinal use, and the company went on to produce a number of other barbiturate compounds as well. Among the derivatives of barbituric acid, about 50 barbiturate compounds became available for medicinal use and were commonly used in psychiatric hospitals and prescribed by general family physicians for sleep, nervousness, and other purposes (Lopez-Muñoz et al., 2005; Shorter, 1997).

We classify barbiturates by time course. Long-acting barbiturates generally take at least one hour to take effect, but produce these effects for 10 to 12 hours. Poor lipid solubility and slow metabolism account for their delayed onset and long length of drug effects. Ultrashort-acting barbiturates produce effects within 10 to 20 seconds and maintain drug effects for approximately 30 minutes. These barbiturates are highly soluble in lipids, quickly store in fats, and rapidly metabolize. We classify barbiturates falling between these time courses as short- or intermediate-acting barbiturates (**Table 8.1**).

Phenobarbital and other barbiturates at the time also were used to aid a general anesthetic, such as *ether*, to induce full anesthesia. In the early 1930s, the barbiturate *hexobarbital* (*Evipal* from Bayer) became the first barbiturate capable of producing general anesthesia (Lopez-Muñoz et al., 2005; Weese & Scharpff, 1932).

**TABLE 8.1** **Barbiturates Classified by Duration for Onset and Duration of Drug Action**

| Class of Barbiturate | Selected Barbiturates | Lipid Solubility | Duration for Onset | Duration of Action |
|---|---|---|---|---|
| Ultrashort-acting | Thiopental (*Pentothal*)<br>Methohexital (*Brevital*) | High | A few minutes | Approximately 30 minutes |
| Short-acting or intermediate-acting | Secobarbital (*Seconal*)<br>Pentobarbital (*Nembutal*) | Medium | Approximately 30 minutes | Approximately 8 hours |
| Long-acting | Phenobarbital (*Luminol*)<br>Mephobarbital (*Mebaral*) | Low | Approximately 1 hour | Approximately 12 hours |

Barbiturates were also the first drugs capable of reducing the frequency and severity of epileptic seizures. They became popular as temporary remedies for stress and anxiety and were readily available for these uses in the first half of the 20th century.

## Drug Profile: ether

| | |
|---|---|
| Other names | Diethyl ether, ethyl ether, ethoxyethane |
| Properties | Activates $GABA_A$ receptors |
| Uses | Once used as a general anesthetic; some modern anesthetics (below), called halogenated ethers, have similar chemical structure (but are non-flammable) |
| Similar drugs | Isoflurane (*Forane*) |
| | Halothane (*Fluothane*) |

## Barbiturates Serve as Drugs of Abuse

During the decades that preceded the 1960s, short-acting barbiturates became commonly abused substances. Users referred to barbiturates as *downers*, among other names. Along with reduced feelings of stress and anxiety, barbiturates produced feelings of well-being and lowered inhibitions.

Barbiturates also appear to have positive reinforcing effects, which are apparent in animals as well as humans. Nonhuman primates readily self-administer barbiturates, for example, and barbiturates increase the breaking points on progressive ratio schedules in animals (Griffiths, Findley, Brady, Dolan-Gutcher, & Robinson, 1975; Morgan, 1990). In human laboratory studies, participants prefer barbiturates just as well as morphine (McClane & Martin, 1976) and short-acting barbiturates more than longer-lasting barbiturates (Morgan, 1990).

**Review!** A break point refers to the maximum number of responses an organism will emit to earn a drug injection (Chapter 5).

## Chronic Barbiturate Administration Increases the Risk of Respiratory Depression

Most deaths occurring from barbiturate overdose result from respiratory depression. Many accidental overdoses likely occurred for those prescribed a barbiturate because of barbiturates' memory-impairing effects, resulting in an individual taking a barbiturate after forgetting that one had been taken earlier (Lopez-Muñoz et al., 2005).

The risk of accidental overdose increases during long-term usage because of a shrinking therapeutic index. Initially, we find a barbiturate's therapeutic dose range far lower than its lethal dose range. However, chronic use causes tolerance to therapeutic effects but not to respiratory depressant effects. As a result, the therapeutic doses shift dangerously close to lethal doses. At this point, even an accidental second administration of a barbiturate might lead to severe respiratory depression.

## Abrupt Withdrawal Causes a Barbiturate Abstinence Syndrome

Abrupt cessation from chronic barbiturate administration can lead to a **barbiturate abstinence syndrome** that is characterized by anxiety, muscle weakness, and abdominal pain. Moreover, in severe cases, seizures may develop, particularly for individuals taking higher doses of barbiturates. Thus, abrupt cessation from regular barbiturate use was dangerous, and those wishing to discontinue barbiturate use had to reduce doses gradually (Westgate & Stiebler, 1964).

**Barbiturate abstinence syndrome**
Anxiety, muscle weakness, and abdominal pain caused by abrupt cessation of barbiturate use

## Barbiturates Produce Pharmacological Effects Through Facilitating GABA Neurotransmission

The key pharmacological action of barbiturates consists of facilitating GABA neurotransmission. Barbiturates do so by binding to a site, appropriately named the *barbiturate site*, on the $GABA_A$ receptor. We find the site pictured on the $GABA_A$ receptor shown in Figure 8.1. Through this site, barbiturates function as a positive modulator, which enhances the inhibitory effects of GABA.

**Review!** A positive modulator is a chemical substance that binds to an allosteric site on a receptor and increases the ability of a neurotransmitter to bind to and/or activate the receptor (Chapter 4).

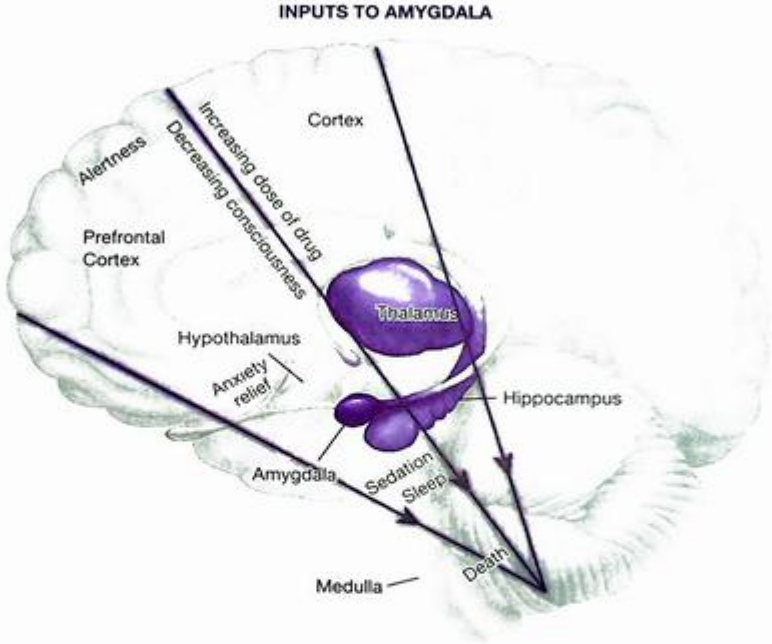
We find $GABA_A$ receptors throughout the brain, but structures of interest here include the amygdala, thalamus, cerebral cortex, and medulla as illustrated in **Figure 8.3**. The anxiolytic effects of barbiturates derive from inhibition of amygdala activity. Inhibition of thalamic and cortical activity accounts for the effects of barbiturates on seizures, memory, attention, and other cognitive functions. The sedative-hypnotic effects of barbiturates occur by suppressing cortical functioning and structures important for cortical arousal. The term **sedative-hypnotic** is used to describe drugs that are calming (i.e., sedative) and sleep inducing (i.e., hypnotic). The effects of barbiturates on respiratory function result from inhibition of the medulla (Ito, Suzuki, Wellman, & Ho, 1996; Meldrum, 1982).

**Sedative-hypnotic**
A drug that produces both calming (sedative) and sleep-inducing (hypnotic) effects

Figure 8.3 also presents a useful concept for relating the dose effects to brain function and pharmacological effects. The concept applies in general to other depressants operating through enhanced GABA neurotransmission as well. The effects of barbiturates become first noticeable on cognitive functioning, including diminished

**FIGURE 8.3** **Brain Structures and Effects of Barbiturates and Other Depressants**

The doses of a CNS depressant such as a barbiturate decrease consciousness as the dose is increased. Alertness is affected first and is linked to suppression of cortical functioning, particularly the prefrontal cortex. A higher dose will provide anxiety relief, resulting from an inhibition of functioning in the amygdala. Even higher doses will affect brain stem areas, resulting in sedation and sleep. If doses are high enough, suppressed activity of the medulla terminates breathing.




attention, impaired decision making, and impaired working memory. We can relate these effects to declined cortical functioning, and Figure 8.3 shows this along a line beginning in the cerebral cortex. Lower doses of barbiturates can exhibit these cognitive effects. Higher doses may be necessary to induce calm by way of inhibiting amygdala function, and much higher doses will impair breathing via inhibition of the medulla.

## STOP & CHECK

1. In humans, the rewarding effects of barbiturates appear equivalent to those of the opioid _____.
2. The major cause of overdose death with barbiturates is _____.
3. The primary mechanism of action for barbiturates is the facilitation of _____ receptor activation by GABA.

1. morphine 2. respiratory depression 3. $GABA_A$

## Benzodiazepines

In 1960, *chlordiazepoxide*, better known by its brand name *Librium*, became the first benzodiazepine drug to reach the market (Tone, 2005) (**Figure 8.4**). During this decade, *Librium* became the most commonly prescribed drug in the United States, only to be surpassed soon after by another benzodiazepine drug, *diazepam (Valium)*.

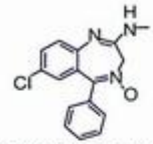
We attribute the discoveries of *Librium* and *Valium* to Leo Sternbach, a chemist working for the chemical company F. Hoffmann-La Roche. These and the dozens of benzodiazepines to follow produced less drowsiness and cognitive inhibition than barbiturates, making them far more appealing for outpatient treatment. These drugs became known as *minor tranquilizers* to note their differences to the barbiturates, which were noted as *major tranquilizers*. In 1981, the Upjohn Company produced *alprazolam (Xanax)*, which remains a commonly prescribed benzodiazepine today. Chemists at Roche discovered *clonazepam (Klonopin)*, which also remains a frequently prescribed drug (Shorter, 1997). Today, we find benzodiazepines to be relatively common drugs; in 2008, for example, an estimated 5.2 percent of U.S. adults had used a benzodiazepine as a prescription for either short-term or long-term use. The majority of benzodiazepine prescriptions came from general practitioners (Olfson, King, & Schoenbaum, 2015).

Like for barbiturates, we also find benzodiazepines characterized by their time course of drug effects. Short-acting benzodiazepines, such as alprazolam and clonazepam, take one to two hours for full effect and have a 12- to 24-hour elimination half-life. Physicians may prescribe these drugs to take as needed for anxiety. Thus, a patient may take these medications when experiencing anxiety or when expecting anxiety. Physicians may also prescribe short-lasting benzodiazepines for insomnia, although newer non-benzodiazepine medications such as *Ambien* serve as first-line treatments for insomnia today. We find intermediate- and long-lasting benzodiazepines used chronically to relieve or prevent generalized anxiety disorder, seizures, and other conditions where long-lasting effects are desired (covered in greater detail in Chapter 14).

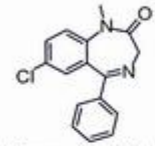
Metabolism accounts for the differences in length of drug action among the benzodiazepines. Unlike short-acting benzodiazepines, intermediate- and long-lasting benzodiazepines produce other benzodiazepines as active metabolites (**Figure 8.5**). In particular, the benzodiazepine drug *nordiazepam* serves as an active metabolite

**FIGURE 8.1 Chemical Structures for Selected Benzodiazepines**

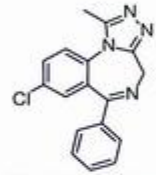
Benzodiazepine drugs share a similar chemical structure.



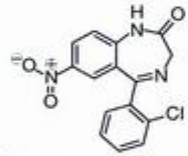

**Chlordiazepoxide (*Librium*)**



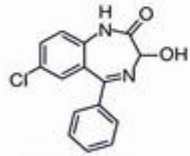

**Diazepam (*Valium*)**




**Alprazolam (*Xanax*)**




**Clonazepam (*Klonopin*)**

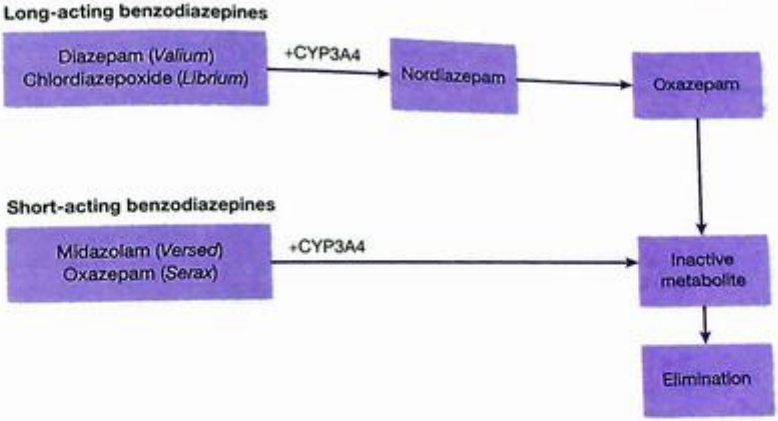



**Oxazepam (*Serax*)**

for many benzodiazepines. Thus, nordiazepam and other active benzodiazepine metabolites produce further benzodiazepine effects. Moreover, enzymes convert nordiazepam to *oxazepam (Serax)*, a short-acting benzodiazepine with no active metabolites (Marin, Coles, Merrell, & McMillin, 2008; Tobin, Lorenz, Brousseau, & Conner, 1964).

**FIGURE 8.5 Illustration of Length of Drug Effects for Selected Benzodiazepines Based on Active Metabolites**

The duration of action for benzodiazepines depends on biotransformation. The two long-lasting benzodiazepines shown here are metabolized in the liver into nordiazepam by CYP3A4 enzymes. Nordiazepam also has benzodiazepine effects, as does its metabolite oxazepam. Oxazepam is also prescribed as a short-lasting benzodiazepine, since it does not have an active metabolite.




*Source:* Data from Marin et al. (1964).

Pharmacogenetic factors also play a role in benzodiazepine metabolism. Benzodiazepines are broken down (i.e., oxidized) primarily by the cytochrome P450 (CYP) enzyme subfamilies CYP-2C19 and CYP-3A4. However, a polymorphism of the CYP-2C19 gene, specifically a CYP-2C19*2 polymorphism, causes poor metabolism of benzodiazepines. As a result, patients with this polymorphism exhibit a stronger and longer-lasting treatment response due to needing a greater length of time to metabolize benzodiazepine molecules. Polymorphisms of the CYP-3A4 gene have not revealed differences in the ability to metabolize benzodiazepines.

The CYP-3A5 enzyme is uniquely involved in metabolism of the benzodiazepines alprazolam and midazolam. Researchers associate a CYP-3A5*3 polymorphism with poor metabolism of alprazolam and subsequently higher levels of alprazolam in blood plasma. This particular polymorphism occurs in approximately 85–98 percent of Europeans, but in only 55–64 percent of African Americans (Tiwari, Souza, & Muller, 2009).

## Risks of Benzodiazepine Use

Like barbiturate drugs, physicians also generally consider benzodiazepines to have abuse potential. However, the positive subjective effects produced by

benzodiazepines may be less than those produced by barbiturates. Griffiths and colleagues (1980) asked human participants to rate how much they "liked" the effects produced by the barbiturate pentobarbital compared to the benzodiazepine diazepam. Consistent with other studies, they reported pentobarbital to be well liked, particularly when compared to diazepam. At the same time, they reported diazepam as somewhat liked, but the degree of liking did not increase as the doses of diazepam increased. Thus, the effects of barbiturates appear more rewarding than the effects of benzodiazepines.

**Benzodiazepine withdrawal syndrome**
A condition caused by abrupt cessation of a chronically used benzodiazepine characterized by anxiety, mania, suicidality, and convulsions

Another reason why benzodiazepines appear to exhibit abuse potential is the development of a **benzodiazepine withdrawal syndrome**, characterized by depression, anxiety, mania, suicidality, and convulsions occurring after abrupt withdrawal of a chronically used benzodiazepine. The withdrawal symptoms of benzodiazepines may last for up to several months. A lower probability of this withdrawal syndrome occurs after gradually reducing the dose of a benzodiazepine over time. The appearance of physical dependence along with inferences that benzodiazepines act similarly to barbiturates support a notion that benzodiazepines have abuse potential.

Kan, Breteler, and Zitman (1997) sought to determine the prevalence of an addiction to benzodiazepines among general practice or psychiatric out-patients taking benzodiazepines at least once a week. The researchers surveyed for features of a benzodiazepine use disorder using both the DSM (at this time, the DSM-III) and the ICD-10, which in addition to the DSM criteria included "craving" as a criterion for diagnosis. They found that 51 percent of general practice and 69 percent of psychiatric patients met the DSM criteria for an addiction to benzodiazepines at some point in their lifetimes. The rates were similarly high when using ICD-10 criteria. When looking at specific features of these diagnoses, the majority of patients had experienced withdrawal symptoms and an impaired ability to reduce use.

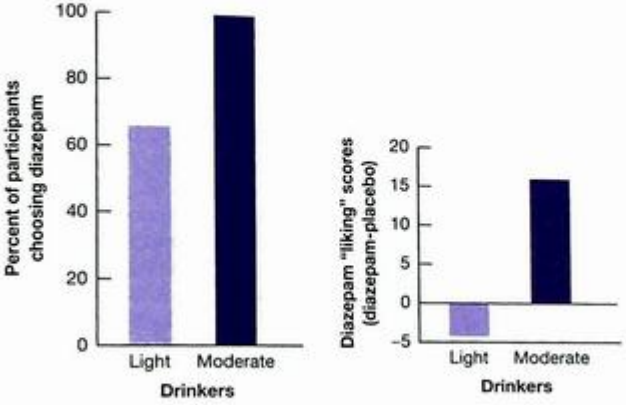
Craving was especially high in this study, with 85 percent of general practice and 94 percent of psychiatric patients describing a craving for benzodiazepines at some point in their lives. A later study conducted to specifically examine craving among benzodiazepine users found that those who experience craving for benzodiazepines generally had a greater severity of benzodiazepine use disorder symptoms and a greater negative mood (Mol et al., 2005). Together, these findings indicate that craving occurs for many individuals during long-term use, especially when an individual develops other signs of benzodiazepine abuse. The DSM-5 now considers craving as one of the diagnostic features of a benzodiazepine use disorder (American Psychiatric Association, 2013a).

One's history of using other substances significantly increases the risk of misusing benzodiazepines (Brunette, Noordsy, Xie, & Drake, 2003). Routine users of GHB have indicated that the benzodiazepine flunitrazepam produced rewarding subjective effects (Abanades et al., 2007). Further, moderate alcohol drinkers, far more than light alcohol drinkers, prefer the effects of benzodiazepine pills compared to placebo and report liking these effects (de Wit, Pierri, & Johanson, 1989) (**Figure 8.6**).

Other risks of benzodiazepines occur from accidental injury, poor decision making, or consuming other drugs when under the effects of a benzodiazepine. We find an increased likelihood of emergency room visits and hospital admissions due to accidental injuries while taking benzodiazepines (Oster, Huse, Adams, Imbimbo, & Russell, 1990).

**FIGURE 8.6** **Assessment of Liking a Benzodiazepine's Effects Among Light and Moderate Drinkers**

Compared to light drinkers, moderate drinkers preferred the benzodiazepine diazepam (*Valium*) over placebo (left) when given the ability to choose diazepam (right) and when indicating how well they liked diazepam on a "liking" scale.




*Source:* Data from de Wit et al. (1989).

Researchers find increased traffic accidents, as well as injuries from these accidents, occurring in people who had taken a benzodiazepine prior to driving (Neutel, 1995).

Among potential drug combinations with benzodiazepines, we find most misuse occurring from combining a benzodiazepine with alcohol. The combined use of these substances, in particular, corresponds to greater rates of drug-induced death; harm caused by drug overdose; and higher rates of accidental injury, including major traffic accidents (Chan, 1984). As noted in the chapter on alcohol (Chapter 9), we can think of this drug combination as magnifying the CNS depressant effects of alcohol (or vice versa), increasing the likelihood of poor decision making and impairing cognitive and motor functions.

## STOP & CHECK

1. Like barbiturates, _____ also are characterized by their time of onset and duration of their drug effects.
2. Polymorphism of the CYP-2C19 gene affects the _____ of benzodiazepines, accounting partly for individual differences in sensitivity to benzodiazepine drug effects.
3. A history of using substances of abuse increases the likelihood of misuse with a _____.

1. benzodiazepines 2. metabolism 3. benzodiazepine

## Benzodiazepines Facilitate GABA Neurotransmission Through Specific Types of $GABA_A$ Receptors

Like barbiturates, benzodiazepines affect the $GABA_A$ receptor, which was shown in Figure 8.1 at the beginning of this chapter. Benzodiazepines serve as $GABA_A$ positive modulators by binding to an allosteric site, referred to as a *benzodiazepine site*, on specific subtypes of the α subunits (Amin & Weiss, 1993; Sigel & Buhr, 1997).

Benzodiazepines have a high affinity for a benzodiazepine site contained within an $\alpha_1$ subunit (Sigel & Buhr, 1997). They have a lower affinity for the benzodiazepine sites contained within $\alpha_2$, $\alpha_3$, or $\alpha_5$ subunits (Klepner, Lippa, Benson, Sano, & Beer, 1979; Pritchett, Luddens, & Seeburg, 1989), and they bind poorly to $\alpha_1$ and $\alpha_6$ subunits (Derry, Dunn, & Davies, 2004; Pritchett et al., 1989). Putting this all together, we essentially have two different types of benzodiazepine sites. We refer to the *high-affinity site*, contained in the $\alpha_1$ subunit, as the **BZ I site**; we refer to the *low-affinity site*, contained in $\alpha_2$, $\alpha_3$, or $\alpha_5$ subunits, as the **BZ II site**.

**BZ I site**
Allosteric site on the $GABA_A$ receptor $\alpha_1$ subunit that a benzodiazepine can bind to; also referred to as the high-affinity site

**BZ II site**
Allosteric site on the $GABA_A$ receptor $\alpha_2$, $\alpha_3$, or $\alpha_5$ subunit that a benzodiazepine can bind to; also referred to as the low-affinity site

As shown in **Figure 8.7**, the locations of these receptors in the brain help explain the behavioral effects of benzodiazepines. We find BZ I sites highly expressed in the cerebellum, substantia nigra, and thalamus (Wisden et al., 1992). Binding to these $GABA_A$ receptors explains why benzodiazepines disrupt balance and coordination (cerebellum), reduce seizure activity, and produce hypnotic effects by inhibiting cortical arousal (substantia nigra and thalamus) (Velísková, Velísek, & Moshé, 1996; Velísková, Velísek, Nunes, & Moshé, 1996). We find BZ II sites highly expressed in the amygdala, hippocampus, and hypothalamus, as well as various parts of the cerebral cortex (Wei, Zhang, Peng, Houser, & Mody, 2003; Wisden et al., 1992).

## Are There Endogenous Benzodiazepines?

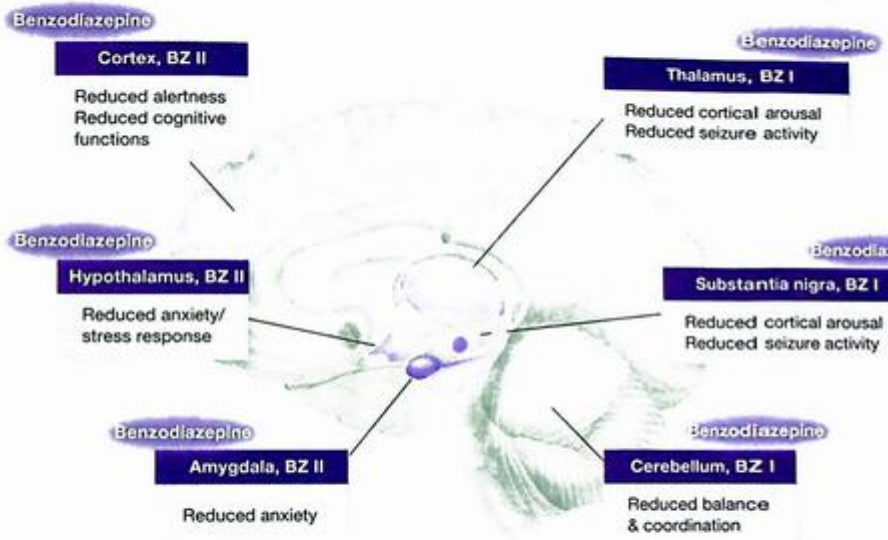
**Endozepines**
Endogenous substances that bind to benzodiazepine sites

Given that sites exist on $GABA_A$ receptors for benzodiazepines, researchers have looked for **endozepines**, endogenous substances that bind to benzodiazepine sites. Endozepines include the protein *diazepam-binding inhibitor* and a family of neuropeptide fragments cleaved from diazepam-binding inhibitor, including *octadecaneuropeptide* and *triakontatetraneuropeptide* (Guidotti et al., 1983; Slobodyansky, Guidotti, Wambebe, Berkovich, & Costa, 1989). In addition, there are a number of endogenous ligands, called *β-carbolines*, which also bind to benzodiazepine sites (Robinson, Anderson, Crosby, Nutt, & Hudson, 2003).

We find endozepines released from astrocytes, and they serve as negative modulators when binding to benzodiazepine sites on $GABA_A$ receptors (Gach et al., 2015; Lamacz et al., 1996; Qian, Bilderback, & Barmack, 2008). In this regard, we can refer to endozepines as *gliotransmitters*, chemical transmitters released from glial cells. The functional significance of endozepines has yet to be firmly determined, but they may have a role in promoting neuronal proliferation by preventing GABA-induced inhibition of neuronal proliferation in the subventricular zone (Alfonso, Le Magueresse, Zuccotti, Khodosevich, & Monyer, 2012). In addition, endozepines may inhibit food intake (Gach et al., 2015; Lanfray et al., 2013). We also find benzodiazepine sites outside of the nervous system, located on mitochondria, where they appear to enhance

**FIGURE 8.7** **Benzodiazepine Receptors in the Brain and Their Effects**

The behavioral effects of benzodiazepines depend on the location of BZ I or BZ II sites in structures throughout the bra




immune system response (Clavier et al., 2014; Krueger, 1995). A number of studies have also shown that β-carboline compounds produce anxiogenic effects (i.e., anxiety-inducing effects) in animal models (Novas, Wolfman, Medina, & de Robertis, 1988).

## STOP & CHECK

1. Benzodiazepines have a greater affinity for the BZ I site, which is found on $\alpha_1$ subunits, and have a lower affinity for the _____ site, which is contained on $\alpha_2$, $\alpha_3$, or $\alpha_5$ subunits.
2. Benzodiazepines reduce seizure activity by binding to BZ I sites on $GABA_A$ receptors in the substantia nigra and _____.
3. What actions do endozepines display for $GABA_A$ receptors?

1. BZ II 2. thalamus 3. They serve as negative modulators.

## Z-Drugs

**Z-drugs (or non-benzodiazepine hypnotics)**
Sleep aids whose generic names usually start with a Z and that act by binding to BZ I sites

**Z-drugs** (or **non-benzodiazepine hypnotics**) consist of sleep aids that act by binding to BZ I sites. The name *Z-drug* refers to the generic names of drugs in this class that typically begin with a *z*. These drugs include *zolpidem (Ambien)*, *zopiclone (Zimovane)*, *eszopiclone (Lunesta)*, and *zaleplon (Sonata)*. We also refer to these drugs as non-benzodiazepine hypnotics to indicate a difference in the chemical structures from benzodiazepines, while also emphasizing their hypnotic effects. Z-drugs have become the most widely prescribed sleep aids in the world (Huedo-Medina, Kirsch, Middlemass, Klonizakis, & Siriwardena, 2012).

Z-drugs all exhibit a high binding affinity for $GABA_A$ receptors that include the $\alpha_1$ subunit (again, referred to as the BZ I site). Some of the Z-drugs also bind with an appreciable affinity for other subunits characterized as the BZ II site. For example, zolpidem, one of the most selective Z-drugs for $\alpha_1\beta_2\gamma_2$ $GABA_A$ receptor, exhibits a moderate affinity for $\alpha_2\beta_1\gamma_2$ and $\alpha_3\beta_3\gamma_2$ $GABA_A$ receptors. Zopiclone, however, exhibits an appreciable affinity for $\alpha_1\beta_2\gamma_2$ and $\alpha_2\beta_1\gamma_2$ $GABA_A$ receptors and a moderate affinity for $\alpha_3\beta_3\gamma_2$, $\alpha_5\beta_3\gamma_2$, $\alpha_5\beta_3\gamma_2$, and $\alpha_5\beta_3\gamma_3$ $GABA_A$ receptors. Thus, we can expect hypnotic effects from positive modulation of $\alpha_1$-subunit-containing $GABA_A$ receptors, and we can also expect other effects from BZ II sites (i.e., $\alpha_2$, $\alpha_3$, or $\alpha_5$ subunit) (Dämgen & Lüddens, 1999).

### Drug Profile: zolpidem

| | |
|---|---|
| Brand name | *Ambien* |
| Properties | Serves as positive modulator for BZ I site $GABA_A$ receptors |
| Uses | Prescribed as a sleep aid |
| Similar drugs | Zopiclone (*Zimovane*) |
| | Eszopiclone (*Lunesta*) |
| | Zaleplon (*Sonata*) |

**Sleep-related complex behaviors**
Complex behaviors that occur while sleeping, including walking, driving, cooking, eating, and carrying on conversations

Hypnotic effects represent the primary pharmacological effects of Z-drugs. Yet, we find a number of other effects from Z-drugs as well. Z-drugs provide a risk, albeit low, of producing **sleep-related complex behaviors** while sleeping. These complex behaviors include walking, driving, cooking, eating, and carrying on conversations all while asleep. The likelihood of these sleep-related complex behaviors increases with Z-drug use (Dolder & Nelson, 2008; Hoque & Chesson, 2009). Z-drugs also can cause imbalance, impair memory, and impair driving. These considerations present a hazard for those who set an alarm to wake up before the effects of the Z-drug wear off, which is why drug manufacturers recommend at least eight hours allotted for sleep (Gunja, 2013).

## Gamma-Hydroxybutyrate (GHB)

**Gamma-hydroxybutyrate (GHB)** is both a drug and a neurotransmitter that has depressant effects on the central nervous system (CNS). GHB is a white, tasteless powder that dissolves easily in water. Depending on the formulation, GHB has both recreational and instrumental uses. As a club drug, GHB goes by many street names, including "Gamma-OH," "Georgia Home Boy," and "Liquid E" (Drug Enforcement Administration, 2012a). GHB earned a negative reputation in the late 1990s as a substance used in sexual assault (ElSohly & Salamone, 1999). The media most often refer to GHB-associated sexual assault as *date rape*, although many of these assaults do not occur during a date and often the victim fails to even recall meeting the assailant. Because of its use as a club drug and in sexual assaults, the Drug Enforcement Administration (DEA) categorized GHB as a schedule I controlled substance in 2000 (Drug Enforcement Administration, 2012b).

**Gamma-hydroxybutyrate (GHB)**
Substance that serves as both a drug and a neurotransmitter that produces CNS depressant effects

Physicians use another formulation of GHB, *sodium* gamma-hydroxybutyrate, as a treatment approved by the Food and Drug Administration (FDA) for **narcolepsy**, a disorder characterized by sudden bouts of daytime heavy sleepiness ("FDA-Approved Labeling for Xyrem Oral Solution," 2005). This formulation, which the DEA assigns as schedule III, goes by the generic name *sodium oxybate* and the brand name *Xyrem*. Although prescribing a depressant to relieve daytime sleepiness may seem strange, researchers find that GHB addresses some of the neuropathological features of narcolepsy, leading to a reduction in its symptoms. More on this later in the chapter.

**Narcolepsy**
A disorder characterized by sudden bouts of daytime heavy sleepiness

Recreational users obtain GHB either by purchasing it from illicit sources or by synthesizing it from **gamma-butyrolactone (GBL)**. Because GBL serves as an immediate precursor to GHB, the DEA categorizes GBL as a schedule I controlled substance. However, given the legitimate uses of GBL in many household products, such as in stains and paint removers, the DEA exempts products containing less than 70 percent of GBL (Drug Enforcement Administration, 2010). We also find small amounts of GHB and GBL in certain red and white wines, vinegar, beer, and coffee (Elliott & Burgess, 2005). As described later in the chapter, GBL serves as a prodrug by metabolically converting to GHB in the body.

**Gamma-butyrolactone (GBL)**
Chemical used in household products that is converted by enzymes to GHB in the body

Approximately 1.4 million individuals 12 and older in the United States reported misuse of GHB in a survey given in 2016 and 2017 (Substance Abuse and Mental Health Services Administration, 2017). Although this rate seems low overall, some areas of the country see more prevalent use. Twenty percent of local and state law enforcement agencies report moderate to high GHB availability (National Drug Intelligence Center, 2004).

### History of GHB

Researchers first synthesized GHB in 1960 as part of an effort to develop compounds with a chemical structure similar to the neurotransmitter GABA. After its discovery, physicians used GHB as an anesthetic agent. In the late 1970s, researchers discovered that the body naturally synthesizes GHB in the central nervous system. In the 1980s, GHB was widely available as a potential supplement for enhancing

muscle growth among weight lifters, although no evidence supports the beneficial use of GHB for this purpose (Andresen, Aydin, Mueller, & Iwersen-Bergmann, 2011; Volpi et al., 1997). Because of concerns over GHB-induced adverse effects, including intoxication and deep unconsciousness, the FDA banned the over-the-counter sale of GHB in 1990 (Woodworth, 1999).

During the 1990s, GHB began to be used in clubs and at parties for its euphoric effects and to improve sociability. The drug was perceived as somewhat similar to alcohol but without inducing hangover (Townsend, 2015). Law enforcement agencies began investigating charges of GHB use in sexual assault. In particular, reports stated that assailants secretly added GHB to alcoholic drinks, strengthening alcohol's and GHB's depressant effects (National Drug Intelligence Center, 2004).

As the association of GHB with clubs and sexual assaults strengthened, local and state governments passed laws regulating and banning its possession and use. During this period, the U.S. Drug Enforcement Administration monitored GHB as a substance of concern; in 2000, the DEA placed GHB on the controlled substances schedule (Drug Enforcement Administration, 2012a). According to law enforcement agencies, the availability and use of GHB has declined significantly since these regulations went into effect (**Figure 8.8**) (Carter, Pardi, Gorsline, & Griffiths, 2009).

## STOP & CHECK

1. GHB, gamma-hydroxybutyrate, is not only a drug but also a _____.
2. To obtain GHB for recreational purposes, what other substances might a user seek?
3. What factors led to the banning of GHB possession and use?

1. neurotransmitter 2. Because GHB is a controlled substance, users may seek compounds such as GBL that serve as prodrugs for GHB. 3. GHB became known for its adverse effects and its use in sexual assaults.

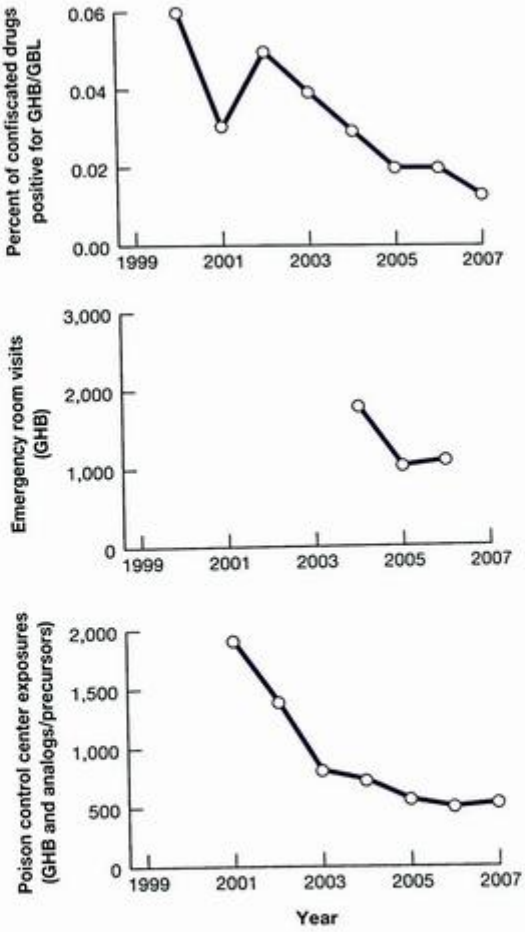
### GHB Is a Drug and a Neurotransmitter

As noted earlier, GHB is both a neurotransmitter synthesized in the CNS and a drug used for therapeutic, recreational, and nefarious purposes. In the body, GHB is a metabolite of the neurotransmitter GABA. The metabolic process begins when the enzyme *GABA transaminase* converts GABA to its metabolite *succinic semialdehyde*. The enzyme *succinic semialdehyde reductase* transforms succinic semialdehyde to GHB (**Figure 8.9**) (Andresen et al., 2011).

As previously stated, certain substances serve as prodrugs for GHB. **Figure 8.10** shows the process of these metabolic reactions for producing GHB. Its primary

**FIGURE 8.8 Declining GHB Use Since Schedule I Categorization**

GHB use has declined sharply since its schedule I categorization in 2000, according to measures of illicit GHB seizure, emergency room visits, and poison control reports.




Source: From Carter, L. P., Pardi, D., Gorsline, J., & Griffiths, R. R. (2009). Illicit gamma-hydroxybutyrate (GHB) and pharmaceutical sodium oxybate (Xyrem®): Differences in characteristics and misuse. *Drug & Alcohol Dependence, 104*, 1–10. doi:10.1016/j.drugalcdep.2009.04.012.

**FIGURE 8.9 Synthesis of GHB From GABA**

GHB is produced naturally in the body through a metabolic process starting with the neurotransmitter GABA.

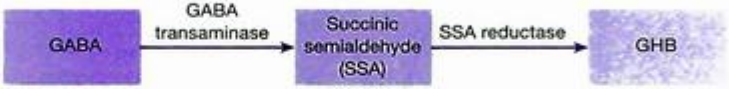



**FIGURE 8.10 Biotransformation of Compounds That Convert to GHB**

The precursor chemicals 1,4-butanediol and GBL can produce GHB through the alcohol metabolic pathway.

**1,4-butanediol** Industrial solvent that produces GBL in the body; GBL subsequently transforms into GHB

prodrugs consist of the chemicals GBL and another substance named *1,4-butanediol*. **1,4-butanediol** is an industrial solvent used in types of plastics and other materials. GBL and 1,4-butanediol are biotransformed in the alcohol metabolic pathway to produce GHB. First, when 1,4-butanediol enters the liver or the stomach, alcohol dehydrogenase converts 1,4-butanediol to GBL. Second, in the liver, the enzyme aldehyde dehydrogenase converts GBL to GHB (Figure 8.10).

As a salt, the drug GHB easily dissolves in liquid. The liquid form of GHB is colorless and tasteless, as is GHB's chemical precursors. The oral delivery of GHB is most common for recreational use and as the form of exposure used in sexual assault cases. The prescription form of GHB, sodium oxybate, is also administered orally, in pill form. Although GHB can be delivered intravenously, this administration route is seldom used. GHB readily penetrates the blood–brain barrier after absorption from the gastrointestinal tract (Andresen et al., 2011). After oral administration in humans, GHB reaches peak levels in blood after 15–45 minutes, and pharmacological effects first occur within 15–20 minutes and last approximately two hours (Carter et al., 2009; Mason & Kerns, 2002).

In the liver and brain, the enzyme GHB dehydrogenase transforms GHB into its own precursor chemical, succinic semialdehyde, which then converts to the neurotransmitter GABA. The elimination half-life for GHB from the body is only 30 minutes. It can remain at detectable levels in blood for only four to eight hours and in

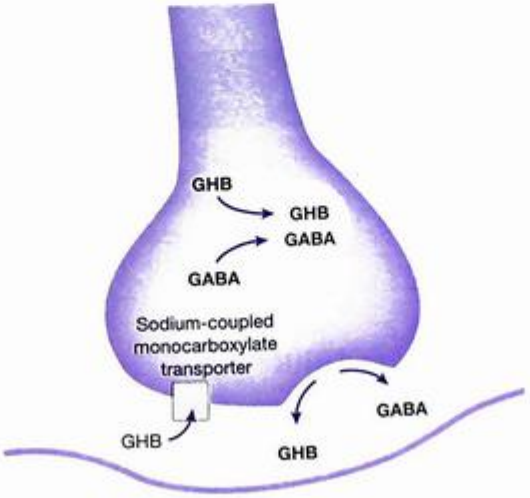
urine for only 8–12 hours. These short elimination periods make determining GHB's use in sexual assault difficult (LeBeau et al., 1999). Although tests confirm GHB use in one to five percent of sexual assaults, the majority of suspected drug-facilitated sexual assault victims present themselves to authorities too late for GHB detection (Zvosec & Smith, 2009). Moreover, standard blood tests conducted after sexual assault do not detect GHB. Instead, victims must notify health professionals that they suspect the use of GHB so that proper tests will be conducted (National Drug Intelligence Center, 2004).

## Pharmacological Actions of GHB

As stated previously, GHB is not only a drug but also a neurotransmitter. The neurotransmitter GHB is found throughout the brain. After synthesis, GHB accumulates within vesicles used for storing GABA. Given that GABA facilitates GHB synthesis and that the same vesicles store both GABA and GHB, many GABA neurons likely release both GABA and GHB (**Figure 8.11**) (Muller et al., 2002).

**FIGURE 8.11** **GHB Neurotransmission**

The synaptic vesicles used for storing the neurotransmitter GABA also store GHB. Subsequently, many GABA neurons may release both GABA and GHB. GHB re-enters neurons through a sodium-coupled monocarboxylate transporter.



Researchers have identified one type of GHB receptor. The GHB receptor is a G-protein-coupled receptor that causes inhibitory effects on neurons. The GHB receptor is found throughout the brain but is highly concentrated in the hippocampus. The cerebral cortex and basal ganglia also exhibit high GHB receptor concentrations (Andriamampandry et al., 2003; Maitre, 1997). Beyond the GHB receptor, studies indicate that GHB binds to a specific subtype of the $GABA_A$ receptor that is composed of $\alpha_4$ and $\beta_1$ subunits (Absalom et al., 2012). Finally, GHB serves as an agonist for the $GABA_B$ receptor (Diana et al., 1991; Pistis et al., 2005). Unlike the $GABA_A$ receptor, the $GABA_B$ receptor is a metabotropic receptor. Through intracellular actions, beginning with activation of a G protein, the $GABA_B$ receptor leads to inhibitory effects on neurons.

GHB re-enters neurons through a *sodium-coupled monocarboxylate transporter* (Figure 8.11) and then rapidly degrades to form GABA, as described previously (Cui & Morris, 2009; Roiko, Felmlee, & Morris, 2012). In fact, although GHB eliminates from the body in 30-minute half-lives, GHB degrades in the brain in five-minute half-lives (Doherty, Stout, & Roth, 1975). Thus, given the rapid degradation to GABA, many of GHB's pharmacological effects may be accounted for by GABA neurotransmission (Wu et al., 2003).

GHB has complex effects on the regulation of dopamine. At low doses in animals, GHB inhibits the firing of dopamine neurons and the release of dopamine from these neurons. High doses of GHB in animals initially produce this same effect, but afterward we find increased dopamine concentrations in the nucleus accumbens and other parts of the basal ganglia (Maitre, 1997). Thus, high doses of GHB exhibit changes in dopamine levels predictive of generating rewarding effects.

## STOP & CHECK

1. GHB is synthesized from the neurotransmitter _____.
2. GHB is an endogenous neurotransmitter that activates GHB and _____ receptors.

1. GABA 2. GABA

## Pharmacological Effects of GHB

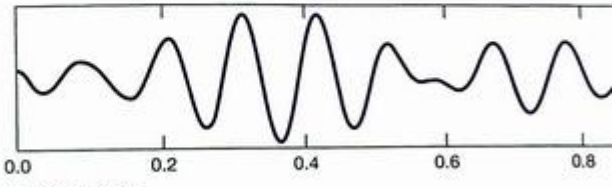
Studies find that GHB has a complex series of pharmacological effects. Early pharmacological studies found that GHB elicits a unique sleeping pattern that is characterized by growth hormone release during the first two hours of sleep and longer periods of deep sleep (**Box 8.1**). The combination of enhanced growth hormone release and deep sleep made GHB an attractive substance for many bodybuilders seeking a substance to enhance muscle repair and growth as well as restorative sleep. However, these purported benefits have not been substantiated (Okun, Boothby, Bartfield, & Doering, 2001).

# BOX 8.1

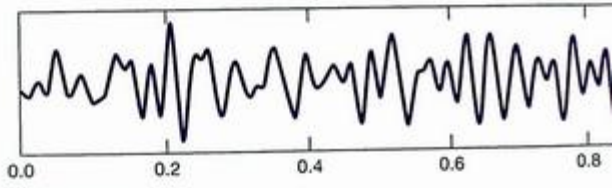
## ELECTROENCEPHALOGRAPHY

**BOX 8.1 FIGURE 1** **Waves Found on EEG Recordings**

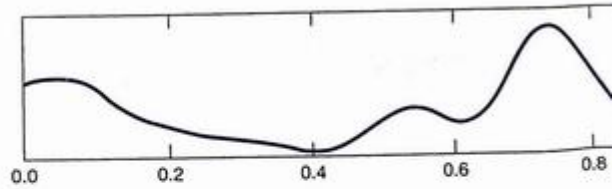
EEG electrodes detect several types of electrical frequencies, presented in *hertz (Hz)*, identif
(b) *beta waves*, (c) *delta waves*, and (d) *theta waves*.



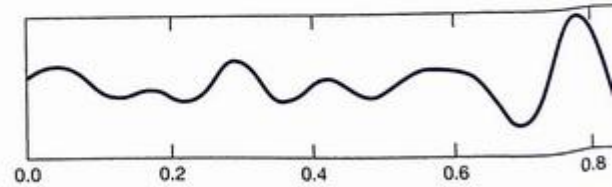

(a) Alpha waves




(b) Beta waves




(c) Delta waves




(d) Theta waves

(Continued)

*Electroencephalography (EEG)* is a method for recording the electrical activity of brain areas through electrodes placed on the scalp. Brain electrical activity is recorded when electrons on the metal of the electrodes on the scalp are moved by electrical changes occurring beneath the electrodes. These electrical changes occur because of exchanges of ions within neurons, particularly ion passage in neuronal axons. Ion passage occurs on neuronal axons during the resting potential when potassium ($K^+$) ions enter and sodium ($Na^+$) ions exit a neuron, during action potentials when $Na^+$ ions rapidly enter a neuron, and during refractory periods when $K^+$ ions exit a neuron. When these electrical events occur among thousands of neurons in a part of the brain at the same time, then these overall electrical changes are detected on EEG electrodes.

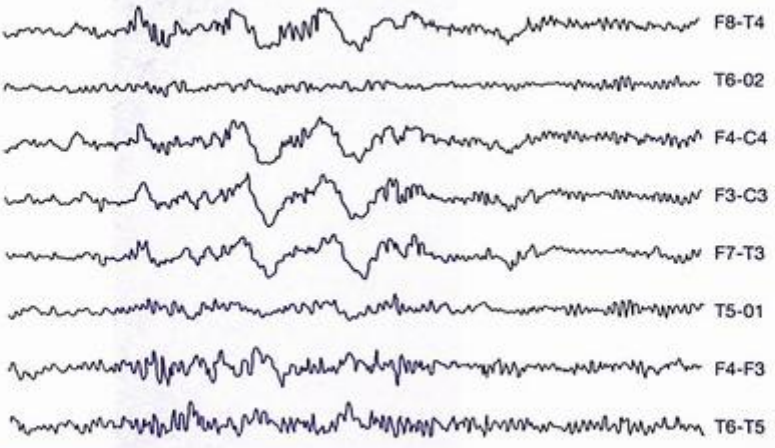
EEG electrodes detect several types of electrical frequencies **(Box 8.1 Figure 1)** presented in *hertz (Hz)*, a value that represents the number of waves produced within a second of time. The *alpha frequency* consists of 8–12 Hz. Alpha waves become larger—that is, have greater amplitude—during relaxation and when eyes are closed. They are prominent during the early stages of sleep. The *beta frequency* is characterized by 12–30 Hz and is low amplitude and irregular during thinking, concentration, movement, and when eyes are opened. Other frequencies, which include *delta* and *theta*, are most often studied during the stages of sleep. Deep sleep, in particular, consists of slow delta and theta waves.

During research or clinical assessment, EEG recordings are made when participants are exposed to some type of stimulus or engaging in a task. An *evoked potential* is an EEG recording during a specific stimulus presentation. An *event-related potential* is an EEG recording during a behavioral or cognitive activity.

Researchers use EEG to study drug effects, such as those produced by CNS depressant drugs. For example, in a study conducted by Metcalf and colleagues (1966), GHB produced a synchronized, slow wave characteristic of a deep sleep. Yet, these slow-wave patterns were seen in awake participants. These findings suggest that GHB inhibits cortical arousal centers such as the reticular formation **(Box 8.1 Figure 2)**.

## BOX 8.1 FIGURE 2 Effects of GHB Studied Using EEG

In awake participants, GHB produced slow-wave bursts characteristic of delta and theta waves (shaded; compare to Box 8.1 Figure 1). Delta and theta waves normally occur during deep sleep.




Source: Adapted from Metcalf et al. (1966).

GHB's effects on growth hormones and deep sleep may have important benefits for narcolepsy. Although narcolepsy is generally considered a disorder of daytime sleepiness, it also consists of fragmented and nonrestorative sleep. These disruptions to nighttime sleeping also lead to deficiencies in growth hormone, which researchers speculate could contribute to this disorder. When given at nighttime, sodium oxybate, the FDA-approved form of GHB, restores growth hormone deficits and increases the length of nighttime sleeping in narcolepsy patients. As a result of improved nighttime sleeping, patients have reduced episodes of sleeping during the day (Donjacour et al., 2011; Okun et al., 2001).

Recreational users characterize three general ranges for orally used GHB doses: "light" doses ranging from 6 to 17 mg/kg, "common" doses ranging from 11 to 28 mg/kg, and "strong" doses ranging from 22 to 51 mg/kg (Oliveto et al., 2010).[1] Studies in controlled laboratory conditions report that GHB increases blood pressure at strong doses; no other appreciable physiological effects occur within these dose ranges (Abanades et al., 2006; Oliveto et al., 2010). GHB's behavioral and subjective effects depend on the dose and the time course. Studies find that strong doses of GHB cause confusion and induce drowsiness (Oliveto et al., 2010). Survey data among GHB users and anecdotal reports suggest that memory loss most often occurs after finishing GHB use, as opposed to during GHB use, for about half of GHB users. Anecdotal reports describe memory-impairing effects seldom occurring for doses as low as 10 mg/kg (Mamelak, 1989; Miotto et al., 2001). Strong doses produce significant impairments in balance as demonstrated when study participants attempt to stand on one foot or perform other motor tasks. Peak effects for these motor effects occur 1 hour after administration (Abanades et al., 2006).

The depressant effects described for GHB in many ways resemble those produced by alcohol. However, GHB does not appear to induce a hangover effect, which is commonly observed from significant consumption of alcohol. Study participants also do not report a dislike for the effects of GHB, whereas participants rate a degree of dislike for some of the effects of alcohol (Johnson & Griffiths, 2013). Clinical trials have shown GHB to reduce withdrawal symptoms in alcohol-addicted patients, suggesting that the similarities between these substances may allow GHB to serve as a treatment for alcohol addiction (Addolorato et al., 1999; Gallimberti et al., 1989).

When sexual predators use GHB in combination with alcohol, the victim appears inebriated and the dual effects of both depressant compounds induce memory loss (i.e., blackout) of the assault (Varela, Nogué, Orós, & Miró, 2004). Those attending bars and clubs can help prevent a drug added to an alcoholic drink by keeping an eye on their beverages and also by carrying *drink test kits*, which come in the form of small paper strips that can detect GHB and many other substances added to a drink. Yet, such tests fail to reach full reliability in laboratory studies (Beyton, Sumnall, McVeigh, Cole, & Bellis, 2006). Therefore, ordering for yourself and watching your drink still serves as the safest approach.

GHB users report positive subjective experiences from GHB use. In a survey conducted by Miotto and colleagues (2001), the majority of regular GHB users reported experiencing euphoria, happiness, increased sexuality, optimism, and other

[1]Amounts converted to mg/kg based on mean weight for U.S. male adults.

positive subjective effects during GHB use. However, this study did not identify the doses used or provide information on the time course for these effects.

GHB studies conducted in laboratory conditions have attempted to relate subjective effects to doses and time course. Stimulant-like subjective effects tend to occur early in GHB's time course, peaking around 45 minutes. During this phase, study participants report feeling stimulated, experiencing amphetamine-like effects, and having feelings of greater energy. They also reported liking the drug's effects. Depressant-like subjective effects tend to occur later in GHB's time course, peaking at around 1.5 hours. During the depressant phase of this time course, participants report feeling drunk, dizzy, drowsy, confused, and sedated (Abanades et al., 2006; Oliveto et al., 2010) (**Table 8.2**).

## STOP & CHECK

1. Why might it be difficult to isolate GHB's overdose effects during an emergency room visit?

1. Users seldom take GHB alone. When overdose occurs, physicians often suspect an interaction between GHB and another substance such as alcohol, which, in particular, may interact with GHB to impair cardiovascular function.

**TABLE 8.2 Time-Dependent Subjective Effects of GHB**

| ~ 45 minutes | 1½ hours |
|---|---|
| Stimulated | Drunk |
| Amphetamine-like effects | Dizzy |
| Greater energy | Drowsy |
| Enjoy the drug effects | Confused |
| | Sedated |

## GHB Overdose and Risk of Addiction

Many of GHB's adverse effects arise from overdose or GHB withdrawal. GHB overdose presents as nausea, unconsciousness, reduced blood pressure, and lowered heart rate. However, most emergency room visits related to GHB, particularly those involving cardiovascular effects, involve the use of other substances, including alcohol or other depressant drugs (Chin, Sporer, Cullison, Dyer, & Wu, 1998). In particular, emergency room admissions due to combined use of GHB or GBL with alcohol tend to involve a nonreactive coma (Liechti, Kunz, Greminger, Speich,

& Kupferschmidt, 2006). An acute withdrawal period follows an episode of GHB use. Most regular users report exhaustion, memory loss, confusion, and clumsiness after GHB use. Some users also report anxiety, insomnia, depression, and dizziness (Miotto et al., 2001).

GHB is uncommon as an addictive substance, since use seldom meets the *Diagnostic and Statistical Manual* (DSM) criteria for a substance use disorder. When GHB use does meet the general DSM criteria, the pattern consists of individuals taking GHB around the clock, about every one to three hours, due to the short half-life of GHB. This manner of use creates a physical dependency that results in the appearance of severe withdrawal symptoms occurring within two to six hours after using GHB. **GHB withdrawal** symptoms include tremor, seizures, memory loss, anxiety, and confusion (Andresen et al., 2011).

**GHB withdrawal**
Withdrawal symptoms occurring within hours of last using GHB that include tremor, seizures, memory loss, anxiety, and confusion

## STOP & CHECK

1. Most emergency room visits due to GHB use likely include what other substance?
2. For a use disorder with GHB, why might a user take GHB every few hours?

1. GHB-related emergency room visits typically include the use of another depressant substance, such as alcohol. 2. GHB has a relatively short half-life.

## Inhalants

**Inhalants** are vaporous chemicals that elicit psychoactive effects. Inhalants represent a large class of compounds that include volatile alkyl nitrites, nitrous oxide, volatile solvents, fuels, and anesthetics (Balster, 1998; Williams & Storck, 2007). The most representative alkyl nitrite consists of **amyl nitrite**, a compound abused in the 1960s and 1970s for its ability to provide feelings of warmth, throbbing sensations, light-headedness, and enhanced sexual experiences (Balster, 1998; Everett, 1972). Users have also referred to amyl nitrite compounds as *poppers* in reference to the sound made when users broke open the small glass ampoules, or vials, containing the drug.

**Nitrous oxide**, also known as *laughing gas*, represents another recreationally used inhalant largely because of its euphoric effects, along with a mixture of depressant and hallucinogenic effects (Balster, 1998). The most common source of nitrous oxide consists of aerosol sprays. In particular, many users inhale nitrous oxide from aerosolized whipped cream containers, which release a puff of nitrous oxide just before releasing whipped cream; users refer to these containers as *whippets* (Howard & Perron, 2009).

By far, the majority of abused inhalants consists of volatile solvents, fuels, and gas anesthetics. The most frequently used compound in this category is *toluene*, but others include gasoline, butane, xylene, and acetone. Many of these chemicals are

**Inhalants**
Vaporous chemicals that elicit psychoactive effects

**Amyl nitrite (or poppers)**
An inhalant recreationally used for feelings of warmth, throbbing sensations, light-headedness, and enhanced sexual experiences

**Nitrous oxide (or laughing gas)**
An inhalant recreationally used for euphoric effects, along with a mixture of depressant and hallucinogenic effects

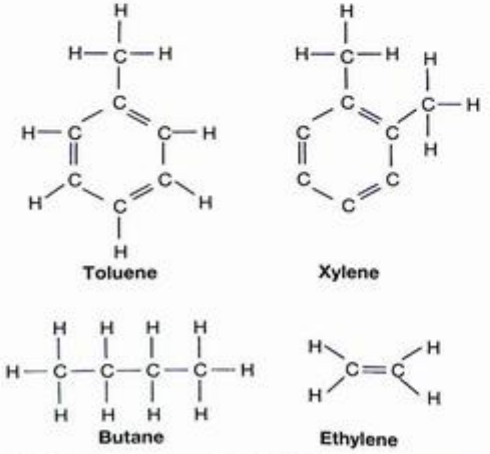
hydrocarbons, referring to their composition of entirely carbon and hydrogen atoms (**Figure 8.12**). These chemicals exist among many household products or in products readily available at hardware stores. Many glues such as model airplane cement contain toluene, and aerosol cans and cigarette lighters contain butane. We find xylene in certain cleaning solutions and in solvents for dissolving oil-based paints. Solutions for dissolving nail polish and paint often contain acetone (Lubman, Hides, & Yucel, 2006).

Adolescents represent the largest portion of inhalant users. Approximately two million adolescents use inhalants, with most inhalant use occurring at age 14. They are the most widely abused drugs for U.S. adolescents below 8th grade, and 12th graders report lower rates of inhalant use, suggesting that inhalant use decreases as adolescents grow up (Johnston, O'Malley, & Bachman, 2003). Researchers find that geographical isolation, poverty, and unemployment represent important risk factors for inhalant abuse, although inhalant abuse is less likely to occur with African American children, children from two-parent households, and children with strong academic performance (Cairney, Maruff, Burns, & Currie, 2002; Nonnemaker, Crankshaw, Shive, Hussin, & Farrelly, 2011).

Beyond the pharmacological effects of inhalants, users find two significant practical aspects that make inhalant abuse relatively easy. First, products containing commonly abused inhalants are legal to purchase. Second, the intoxication users achieve from inhalants wears off quickly, allowing an inhalant to be used after school and then the user can go home sober soon afterward (Cohen, 1977; Kurtzman, Otsuka, & Wahl, 2001).

**FIGURE 8.12 Chemical Structures for Common Inhalants**

Many inhalants are hydrocarbon chemicals, which consist entirely of carbon (C) and hydrogen (H) atoms.



## STOP & CHECK

1. What is the most commonly abused inhalant?
2. In addition to ease of access, what is another practical reason why adolescents abuse toluene?

1. Toluene, which is found in many types of glue 2. The effects of toluene wear off quickly, allowing for an adolescent, for example, to sniff glue after school and then go home sober soon after.

### History of Inhalants

Some instances of inhalant effects can be found in ancient human history. For example, in ancient Greece, Pythia at the Temple of Apollo receded into alcoves that appeared filled by vapors emitted from cracks in the floor in order to provide oracles by communicating with the gods. Modern scholars suspect that these vapor emissions contained ethylene, a known intoxicating agent that causes delirium, disinhibition, euphoria, and even feelings of disembodiment (de Boer, Hale, & Chanton, 2001).

Yet, most of the history of inhalant use comes during the age of modern chemistry. Two of the oldest known psychoactive inhalants are nitrous oxide and ether. After Joseph Priestley discovered nitrous oxide in 1776, Sir Humphrey Davy in the same year discovered that it produced an excited state, hence the name *laughing gas*. Davy gathered together many people for nitrous oxide parties. We attribute the discovery of nitrous oxide's anesthetic effects to Horace Wells, who observed an individual's apparent lack of pain while intoxicated with nitrous oxide and decided to try it out for pulling teeth, albeit with limited success. However, other dentists and physicians perfected its use, and nitrous oxide remains a common anesthetic gas today (Brecher, 1972).

Some of the first reports of inhalant sniffing occurred immediately after World War II (Kerner, 1988). The first scientific report on glue sniffing came out in the *Journal of the American Medical Association* in 1959, which reported on arrests for glue sniffing made in Arizona and Colorado (Glaser & Massengale, 1962). The first major indication of an epidemic came from a report by Bass (1970), who reported 110 cases of sudden death occurring from inhalant abuse. Today, although these remain legal substances because of their use in everyday products, many states and localities have laws banning glue sniffing and the abuse of other inhalants (Brecher, 1972; Williams & Storck, 2007).

## STOP & CHECK

1. Although nitrous oxide first gained notoriety as laughing gas, what was an important therapeutic use of this inhalant?

1. Nitrous oxide exhibits anesthetic effects and eventually became an important anesthetic gas for dental procedures.

## Inhalants: Rapid Absorption and Elimination

Users generally administer inhalants by taking a series of inhalations over 15–20 minutes, briefly achieving inhalant concentrations of more than 6,000 parts per million. Three common approaches to inhaling solvents are called *sniffing*, *huffing*, and *bagging*. Sniffing involves directly inhaling vapors emitted from a small container or a soaked cloth. Huffing involves placing a soaked cloth directly over the mouth or nose, usually to increase the amount of compound inhaled. Bagging consists of a user placing a compound in a small paper or plastic bag and then inhaling the contained vapors (Kurtzman et al., 2001; Lubman, Yucel, & Lawrence, 2008).

Most inhalants offer high lipid solubility, making for rapid absorption and penetration into tissues, including the brain. In animals, intravenous delivery of toluene achieves peak levels in the brain within one to three minutes, and these brain levels of toluene reduce by half after approximately 20 minutes. However, toluene eliminates more slowly from white matter in the brain and reduces by half after 30 minutes (Gerasimov, 2004). As described previously, the rapid elimination of inhalants offers an important practical appeal to adolescents who might seek to sober up before going home after school.

## Pharmacological Actions of Inhalable Solvents

As already noted, inhalants represent a large class of diverse compounds that leads to a variety of different pharmacological actions. This chapter focuses on the actions of toluene and related inhalable chemicals because these are the most commonly abused inhalants. Toluene and most other inhalants elicit depressant effects through mechanisms shared with alcohol (Chapter 9), including antagonism of NMDA receptors and positive modulation of $GABA_A$ receptors.

Acute toluene administration acts as a noncompetitive antagonist for NMDA receptors, eliminating the flow of ions through the NMDA channel (Cruz, Mirshahi, Thomas, Balster, & Woodward, 1998). Several days of repeated toluene exposure leads to an increase in NMDA receptors, suggesting a potential mechanism for pharmacodynamic tolerance (Bale, Tu, Carpenter-Hyland, Chandler, & Woodward, 2005). Acute toluene administration also increases the activation of $GABA_A$ receptors by serving as a positive modulator. Repeated administration of toluene results in decreased activation of $GABA_A$ receptors, also serving as a form of pharmacodynamic tolerance (Bale et al., 2005; Beckstead, Weiner, Eger, Gong, & Mihic, 2000).

Microdialysis studies evaluating toluene's ability to enhance nucleus accumbens dopamine levels provide mixed results. Gerasimov and colleagues (2002) did not find changes in dopamine concentrations in the nucleus accumbens in rats exposed to 3,000 parts per million of toluene. However, Riegel, Zapata, Shippenberg, and French (2007) found increased dopamine concentrations in the nucleus accumbens in rats after administration of toluene directly into the ventral tegmental area. Yet, these authors found that dopamine occurred at a specific dose of toluene; above or below this level, doses failed to increase dopamine concentrations in the nucleus accumbens.

## Inhalants: Pharmacological Effects and Interference With Oxygen Intake

Like many other depressant drugs, toluene and other inhalants initially exhibit stimulant-like effects and later exhibit depressant-like effects. From reviewing numerous clinical studies on acute inhalant effects, Kurtzman and colleagues (2001) describe four general stages of inhalant effects (**Table 8.3**). The *first stage* begins within a few minutes after inhalation. During the first stage, an inhalant elicits stimulant-like positive subjective effects, including excitation, euphoria, and exhilaration. In studies examining mice, we find increased locomotor activity in an open field after administration of lower concentrations of an inhalant (Bowen & Balster, 1998).

The *second stage* consists of many behavioral effects that resemble alcohol intoxication. The behavioral effects include disorientation, slurred speech, and confusion. However, unlike general alcohol intoxication, toluene may also produce hallucinations, particularly during frequent use (Cruz & Dominguez, 2011). The *third stage* of inhalant intoxication consists of further depressant effects, including a blunting of sensations and poor motor coordination. In mice, we find that higher concentrations of inhalants lead to suppressed locomotor activity in an open field (Bowen & Balster, 1998).

Depending on the amount of inhalant administered, users may also experience a *fourth stage* of intoxication that consists of **inhalant overdose**, a condition characterized by a series of adverse effects, including stupor, seizure, unconsciousness, cessation of breathing, and cardiac arrest. Cardiac arrest serves as the primary cause of **sudden sniffing death syndrome**. Poor oxygen availability occurs when inhalant vapors compete with the inhalation and absorption of oxygen. Low oxygen levels significantly impair brain and cardiovascular function. Sudden sniffing death syndrome can occur when someone is startled while highly intoxicated with an inhalant. In particular, this may occur if an adolescent sniffing glue is caught by a parent. Oxygen delivery serves as the primary treatment for treating inhalant overdose (Alper et al., 2008; Kurtzman et al., 2001).

**Inhalant overdose**
Overdose from inhalant use characterized by a series of adverse effects that can include stupor, seizure, unconsciousness, cessation of breathing, and cardiac arrest

**Sudden sniffing death syndrome**
Death occurring from inhalant overdose

**TABLE 8.3 Stages of Inhalant Effects**

| Stage | Effects |
|---|---|
| 1 | Stimulant-like positive subjective effects, including excitation, euphoria, and exhilaration |
| 2 | Behavioral effects that include disorientation, slurred speech, and confusion; hallucinations may occur |
| 3 | Enhanced depressant effects, including blunted sensations and impaired motor coordination |
| 4 | Overdose consisting of stupor, unconsciousness, seizures, breathing cessation, and cardiac arrest |

Chronic heavy use of inhalants can produce severe neural damage, including cortical white matter degeneration and ventricle enlargement, an indicator of brain tissue loss (Rosenberg, Grigsby, Dreisbach, Busenbark, & Grigsby, 2002). This damage is consistent with a study conducted by Hormes, Filley, and Rosenberg (1986) that examined chronic users of high concentrations of toluene for more than two years. Most of these individuals exhibited severe cognitive impairment, muscle weakness, tremor, poor eye tracking, poor hearing, and a poor sense of smell.

Yuncu and colleagues (2015) conducted a series of neurological assessments in adolescents (generally defined as ages 10 to 19) who used inhalants nearly every day for at least six months. Using *diffusion tensor imaging*, an MRI method that assesses the structural orientation of cells based on water diffusion, they found reduced integrity of white matter tissue in the parietal, occipital, and temporal lobes. Further, these users performed poorly on a Wisconsin Card Sorting Task, a test of executive functioning, and a Stroop test, a test of processing speed, compared to a control group of adolescents who did not use inhalants.

According to the DSM-5, chronic inhalant use may also develop into an inhalant use disorder. A user with an inhalant use disorder may exhibit tolerance as defined by requiring greater amounts of an inhalant to achieve the same effect. Although the DSM defines inhalant use disorder as being similar to most substance dependence disorders, it states that withdrawal symptoms either do not occur or are generally mild and not clinically significant (American Psychiatric Association, 2013a). In a study by Ridenour, Bray, and Cottler (2007), however, 11 percent of inhalant-dependent users described experiencing headaches, nausea, hallucinations, craving for an inhalant, depressed mood, and fast heartbeat as time passed after inhalant use. These authors also noted that unlike most substance dependencies, withdrawal symptoms most likely occur after a binge with inhalants and tend to last for only one or two days.

## STOP & CHECK

1. What is the primary pharmacological action of inhalable solvents?
2. The primary adverse physiological effects of inhalable solvents result from competition with _____.
3. What types of brain damage occur during long-term inhalant use?

1. Inhalable solvents facilitate activation of GABA receptors. 2. oxygen 3. Researchers find degeneration of cortical white matter and enlarged ventricles.

## From Actions to Effects: Stimulus Properties of GHB and Toluene

As first presented in Box 6.1, drug discrimination procedures provide the ability to determine similarities among the subjective effects of different drugs. Researchers

also use this procedure to determine the role different receptor actions may play in a drug's subjective effects. Drug discrimination procedures provide important information on the receptor actions for depressant drugs.

Cook, Biddlestone, Coop, and Beardsley (2006) conducted a drug discrimination study using mice trained to discriminate a dose of GHB versus saline. After the mice learned to perform this discrimination accurately, the researchers gave the mice doses of alcohol to determine which lever the mice would choose. When given alcohol, some mice responded on the GHB lever, but others responded on the saline lever, suggesting to these researchers that alcohol's subjective effects only somewhat resemble GHB's subjective effects.

As an important next step in this research area, Baker, Searcy, Pynnonen, and Poling (2008) conducted a three-lever drug discrimination procedure that required rats to discriminate alcohol for one lever, versus GHB for another lever, versus saline for the third lever. In this way, rats had to attend to the different subjective effects between alcohol and GHB to accurately learn this procedure. After the rats achieved a high rate of accuracy in performance, these researchers conducted a series of tests to determine the receptors important for the discriminative stimulus effects for these compounds.

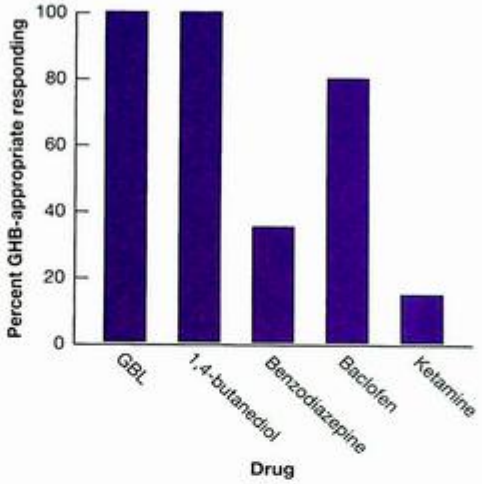
This study by Baker and colleagues (2008) provided several interesting findings about the discriminative stimulus effects of GHB (**Figure 8.13**). *First*, both GBL and 1,4-butanediol led animals to respond on the GHB-appropriate lever, probably because GBL and 1,4-butanediol convert to GHB in the body through metabolic processes. Second, a benzodiazepine drug, which functions as a $GABA_A$ positive modulator, led to more responses on the alcohol lever and few responses on the GHB lever, suggesting that $GABA_A$ receptors important for the subjective effects of benzodiazepines are not important for the subjective effects of GHB. Third, administration of the $GABA_B$ receptor agonist baclofen led animals to press the GHB lever, which supports pharmacological evidence that GHB acts as a $GABA_B$ receptor agonist. Finally, when the researchers administered the NMDA receptor antagonist ketamine, rats mostly responded on the alcohol lever rather than the GHB lever. This also supports known pharmacological evidence, because alcohol serves as an antagonist at NMDA receptors (covered in Chapter 9), whereas GHB appears devoid of NMDA receptor effects.

Drug discrimination findings also correspond with the pharmacological actions of toluene. For example, Rees, Knisely, Jordan, and Balster (1987) trained mice to discriminate toluene, which was injected as a liquid solution, from the drug's vehicle. They first verified that mice would press the toluene lever and administered toluene via inhalation. After verifying this, they found that administration of the $GABA_A$ receptor positive modulator pentobarbital led to toluene lever responding. This finding coincides with toluene's positive modulation of $GABA_A$ receptors.

In a separate study, Shelton and Balster (2004) trained mice to discriminate an NMDA receptor antagonist, dizocilpine, from saline in a drug discrimination task. Although toluene exhibits antagonism of NMDA receptors, the mice failed to choose the dizocilpine lever after toluene administration. The researchers concluded that NMDA receptor antagonism may not be important for toluene's subjective effects.

**FIGURE 8.13 Drug Discrimination Results With GHB**

Drug discrimination experiments reveal receptor actions important for GHB's subjective effects. For simplicity, this figure only shows the percentage of responses occurring on the GHB-appropriate lever (*y*-axis). See text for further details on this study.




*Source:* Data from Baker et al. (2008).

## STOP & CHECK

1. What do drug discrimination procedures tell us about the subjective effects of GHB?
2. What mediates the stimulus properties of toluene?

1. Although pharmacological procedures determine the receptor actions of psychoactive drugs, drug discrimination procedures link these receptor actions to a drug's subjective effects. For GHB, we learn that activation of $GABA_B$ receptors contributes to its subjective effects. We also learn that the prodrugs GBL and 1,4-butanediol also produce GHB-like subjective effects, likely by producing GHB through metabolism. 2. Based on drug discrimination procedures, positive modulation $GABA_A$ receptors elicit toluene-like stimulus properties.

## CHAPTER SUMMARY

Depressant drugs diminish physiological activity and cortical arousal. Many depressant drugs exhibit positive subjective effects, facilitating recreational use and abuse of these substances. Commonly used depressant drugs include alcohol, benzodiazepines, barbiturates, opioids, and cannabinoids. Most depressant drugs exert their effects through enhancing GABA neurotransmission, or through $GABA_A$ receptors. Barbiturates and benzodiazepines act directly on the $GABA_A$ receptors to produce depressant effects. Sleep aids known as Z-drugs act on specific subtypes of the $GABA_A$ receptor to induce sleepiness. GHB is both a drug and a neurotransmitter that produces depressant effects. The drug is colorless and tasteless and is used as a recreational substance, a sexual assault drug, and a treatment for narcolepsy. Because GHB is a controlled substance, many users instead seek one of GHB's prodrugs, GBL or 1,4-butanediol. Neurotransmitter synthesis of GHB begins with the inhibitory neurotransmitter GABA. GHB is stored in vesicles with GABA; when released, it binds to and activates GHB receptors, specific subtypes of the $GABA_A$ receptor, and $GABA_B$ receptors. The pharmacological effects of GHB include prolonged deep sleep, confusion, drowsiness, and memory impairment as well as positive subjective effects such as euphoria and optimism.

Inhalants include volatile alkyl nitrites, nitrous oxide and volatile solvents, fuels, and anesthetics, among which toluene is the most used. Adolescents serve as the majority of inhalant users. Inhalants absorb rapidly, readily penetrate tissues, and have short-lasting effects. Their pharmacological actions depend on antagonism of NMDA receptors and positive modulation of $GABA_A$ receptors. Inhalants produce a time-dependent course of stimulant and depressant effects. Inhalant overdose may lead to sudden sniffing death syndrome, and long-term inhalant abuse may damage parts of the brain.

## KEY TERMS

Depressant 244
$GABA_A$ receptor 244
Barbiturate abstinence syndrome 249
Sedative-hypnotic 249
Benzodiazepine withdrawal syndrome 254
BZ I site 256
BZ II site 256
Endozepines 256
Z-drugs (or non-benzodiazepine hypnotics) 258
Sleep-related complex behaviors 258
Gamma-hydroxybutyrate (GHB) 259
Narcolepsy 259
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1,4-butanediol 262
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Amyl nitrite (or poppers) 269
Nitrous oxide (or laughing gas) 269
Inhalant overdose 273
Sudden sniffing death syndrome 273

CHAPTER 9

# Alcohol

## Chapter Outline

- Alcohol: The Most Commonly Used Depressant Substance
- Alcohol Production Through Fermentation and Distillation
- History of Alcohol
- Pharmacokinetic Factors and Alcohol's Effects
- Alcohol and Interactions With Other Drugs
- Alcohol and Central Nervous System Functioning
- Pharmacological Effects of Alcohol
- Treating Alcohol Addiction
- From Actions to Effects: Hangover

## Learning Objectives

- Describe the forms and origins of beverage alcohol
- Evaluate the role that pharmacokinetics play in the effects of alcohol
- Evaluate the effects of alcohol and relate these effects to its pharmacological actions
- Assess the features of alcohol use disorder and examine pharmacological approaches for treatment

## Alcohol: The Most Commonly Used Depressant Substance

**Ethyl alcohol (or ethanol)**
An alcohol that functions as a central nervous system depressant

**Methyl alcohol (or methanol)**
An industrial solvent that acts as a toxin for optic nerves and can be produced during the distillation process for moonshine

Beverage alcohol consists of any drink containing **ethyl alcohol**, also known as **ethanol**, a central nervous system (CNS) depressant. We regularly contact other forms of alcohol, but these types are not safe to drink. One of these types is *isopropyl alcohol*, or *isopropanol*, which is commonly known as *rubbing alcohol*. Another type is *methyl alcohol*, or *methanol*. **Methyl alcohol**, or **methanol**, is an industrial solvent used in many products, including antifreeze. Methyl alcohol acts as a toxin for optic nerves and can be produced during the distillation process for *moonshine;* if consumed, it causes blindness.

Beverage alcohol is widely consumed across the world, second only to caffeine. According to the World Health Organization, approximately two billion people a year consume alcoholic beverages, and approximately 76 million individuals have an alcohol use disorder such as alcohol addiction. Alcohol consumption per capita varies across countries. The highest alcohol consumption levels occur in Europe, the Russian Federation and former Soviet states, North America, South America, and Australia. The Middle East reports the lowest levels of alcohol consumption (World Health Organization, 2014).

According to a 2014 survey conducted by the Substance Abuse and Mental Health Services Administration (SAMHSA), more than half of all U.S. individuals 12 and older reported being current consumers of alcohol, and 81.5 percent reported ever consuming alcohol. We tend to find current alcohol use slightly higher for men (57.3 percent) than women (48.4 percent). The youngest of those surveyed, 12- to 17-year-olds, represent approximately 11.5 percent of alcohol consumers (Center for Behavioral Health Statistics and Quality, 2014b).

## Alcohol Production Through Fermentation and Distillation

**Percentage alcohol (or alcohol by volume)**
Number of grams of alcohol found in 100 milliliters of solution

**Proof of alcohol**
Numerical value that is double the percentage of alcohol

**Fermentation**
Alcohol production using yeast cells and some type of starch such as grain or fruit

Beer, wine, and spirits serve as the primary sources of beverage alcohol. Small amounts of alcohol are also found in vinegar, leftover from the production of acetic acid from ethanol, and certain liquid medications such as cough syrups.

The amount of alcohol in a beverage is labeled in two ways: by percentage and by proof. **Percentage alcohol**, also known as **alcohol by volume**, refers to the number of grams of alcohol found in 100 milliliters of solution. For example, 50 g of alcohol in 100 ml of solution equates to 50 percent. The **proof of alcohol** is a numerical value that is double the actual percentage of alcohol. For example, a beverage with 50 percent alcohol is 100 proof.

Alcoholic beverages vary in percent alcohol content, depending on whether brewers used a fermentation method or a distillation method. **Fermentation** is a process of alcohol production using yeast cells and some type of starch such as grain or fruit. During fermentation, yeast interacts with sugars from starches, creating alcohol. The longer that yeasts have to metabolize these sugars, the greater the percentage of alcohol produced. The approximate upper limit for alcohol production using

fermentation is 15 percent. Higher alcohol percentages kill yeast cells, causing fermentation to end.

Most beers and wines contain less than 15 percent alcohol. **Beer** is an alcoholic beverage, usually with five percent or less alcohol content, made through fermentation of certain types of starch such as barley, wheat, or rice. During the fermentation process, brewers add other ingredients such as hops and fruit to further promote fermentation and provide flavoring. *Indian pale ales* (typically referred to as IPAs) are noted for strong hops flavorings. Most commercial domestic beers are made from barley and hops and contain about five percent alcohol. *Malt liquor*, although actually beer, comes from malted barley and contains more than five percent alcohol due to having more sugars added to enable further alcohol production from fermentation. Some countries are known for unique varieties of beer. Belgium, for example, produces fruitier beers, and Japan produces rice beers, such as *Saké*.

**Beer**
An alcoholic beverage, usually with five percent or less alcohol content, made through fermentation from certain starches such as barley, wheat, or rice

**Wine** is an alcoholic beverage, usually with 12–15 percent alcohol content, made through fermentation of fruit. Most winemakers use grapes, which provide a sugar source, along with certain acids, enzymes, and nutrients during the fermentation process. Beyond grapes, some winemakers use other fruits such as strawberries or cherries. Wines made from fruits other than grapes are called *fruit wines*.

**Wine**
An alcoholic beverage, usually with 12–15 percent alcohol content, made through fermentation of fruit

Another alcoholic beverage is kombucha. *Kombucha* blends consist of brewed teas that contain alcohol. Alcohol fermentation occurs by adding yeast to the tea. This typically produces a one percent alcohol beverage, although longer brewing times can increase this to three percent (Mayser, Fromme, Leitzmann, & Gründer, 1995).

**Distilled alcoholic beverages** (also referred to as *liquors* or *spirits*) are produced through distillation and have a higher alcohol content than beers and wines. Distillation is a method that separates alcohol from a fermented mixture. During this process, distillers heat a fermented mixture until it exceeds alcohol's boiling point. At this boiling point, alcohol evaporates; the alcohol vapors are routed through tubes into a cooler compartment where the alcohol returns to a liquid form, making a highly concentrated alcoholic solution.

**Distilled alcoholic beverages**
Alcoholic beverages produced through distillation that have a higher alcohol content than beer and wine

Distilled alcoholic beverages tend to contain at least 20 percent alcohol and come in many different varieties such as brandy, gin, rum, tequila, vodka, and whiskey. The different flavors born from distillation depend on the starch used in fermentation, the filtration methods used to purify the alcohol collected during distillation, and the method of storage. In other words, along with the distilled alcohol, other chemicals collect in the fermented brew, and the desired flavor in part depends on the filtration of these chemicals from the distilled solution and the type of container in which the end product is aged or stored.

One of the purest distilled spirits is a grain-based alcohol marketed as Everclear. Everclear is highly filtered so that it contains a high concentration of alcohol with few other chemicals. The varieties of Everclear vary from 75 percent to 95 percent alcohol. The highest concentration version is illegal to sell in some U.S. states. Vodka consists of another highly filtered distilled spirit that may be based on grains or other starch sources. Although many vodkas contain around 50 percent alcohol, other varieties of vodka may contain as much as 95 percent. Brandy, whiskey, and rum typically contain 40–60 percent alcohol and vary in flavor.

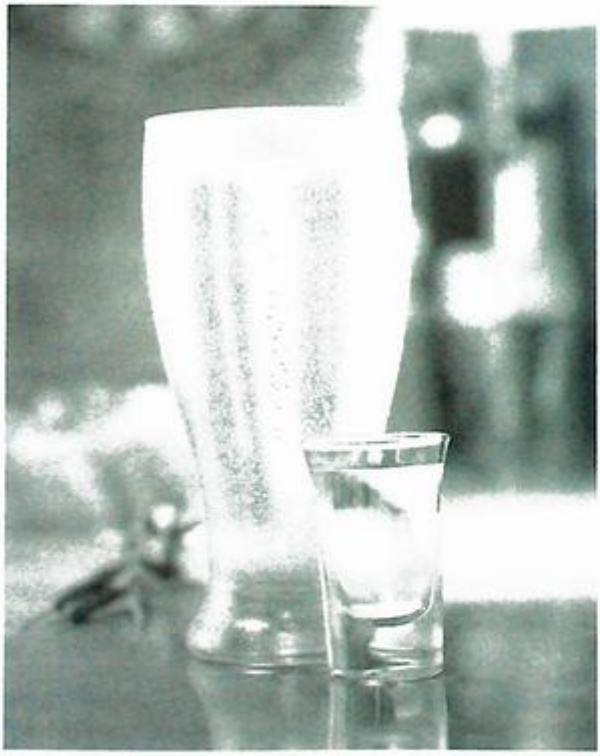
Home distillation is illegal in most U.S. states. These methods produce a beverage often referred to as *moonshine*. Home distillation methods, however, are notorious for dangerous impurities, including methanol as noted earlier.

**Standard drink**
Drink that contains 14 grams of 100 percent alcohol; equivalent to about 2/3 fluid ounces

Given the enormous variety of alcohol concentrations among beverages, health officials compare beverages according to standard drink units. A **standard drink** contains 14 grams of 100 percent alcohol, which is equivalent to about 2/3 of a fluid ounce. To put this in perspective, a small shot glass holds about 1½ fluid ounces. A standard drink equivalent of 190-proof Everclear (95 percent alcohol) fills about half of a small shot glass. A standard drink equivalent of whiskey is approximately 1½ fluid ounces and fills a small shot glass. For a typical domestic beer, the standard drink equivalent consists of 16 ounces or one pint (National Institute on Alcohol Abuse and Alcoholism, 2012) (**Figure 9.1**).

**FIGURE 9.1 Standard Drink Comparisons**

Standard Drink Comparisons Between Whiskey and Domestic Beer



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## STOP & CHECK

1. Of the many types of alcohol, which is safe to drink (in moderation)?
2. If an alcoholic drink is 40 percent alcohol, what is the proof?
3. Although fermentation can produce as much as 15 percent alcohol, higher concentrations can be achieved using _____.
4. Alcoholic beverages are compared for alcohol content by referring to _____ drinks, which are equivalent to 14 grams of 100 percent alcohol.

1. ethyl alcohol, also known as ethanol 2. The proof of an alcoholic beverage is double the percentage of alcohol. A 40 percent alcoholic drink is 80 proof. 3. distillation 4. standard

## History of Alcohol

Scholars hypothesize that early Neolithic peoples raised and fermented grapes as early as 6000 B.C. The recorded history of alcohol dates to Sumerian writings in 3200 B.C. During this period, early taverns in Sumer and Egypt sold alcohol, and traders transported alcohol throughout the known world.

Both wine and beer were described during this age. Wine was a limited commodity and considered a drink of luxury for consumption by ruling figures. Sumerian writings describe a beer made from barley. Egyptian writings describe many types of beer made from barley as well as a beer called *hek* made from honey. In both Sumer and Egypt, beer making was common in households, and the recreational use of beer was a normal part of everyday life.

Opposition to alcohol also existed during this time. In 2000 B.C., an Egyptian priest wrote a letter to one of his pupils, stating "I forbid thee to go to the tavern. . . . Thou are degraded like the beasts." The Code of Hammurabi, written around 1750 B.C., regulated drinking establishments called "wine shops" to prevent riotous gatherings.

Aside from recreational purposes, the Sumerians also used alcohol as a vehicle for many medicines. Around 800 B.C., Greeks used wine in religious ceremonies and to treat pain. Moderate drinking occurred soon after Rome's founding around 750 B.C. However, rampant drinking began around 200 B.C. and was a hallmark of Roman culture through its fall around A.D. 200. By this time, alcohol consumption was a normal part of European life.

Distilled alcohol arrived around A.D. 1250, mostly as an expensive medicine, and its lauded benefits led to the term *aqua vitae*, the water of life. The sense of youth, vitality, and physical well-being led to describing distilled alcohol as a *spirit*. Brandy was the primary spirit consumed until around the late 1400s, when a Scottish publication described a recipe for whisky made from malted barley rather than wine. In 1550, a publication in Holland described the first recipe for gin. Rum was popular in colonial America because of its low production cost and the triangle trade that brought inexpensive sugar cane to the colonies.

Many alcohol-related adages have their origins in this period. In England, public houses—*pubs*—served alcoholic drinks in pints and quarts. The oldest pub in English history is Ye Olde Fighting Cocks, which was established sometime in the 12th century and still operates today. The phrase "Mind your p's and q's," meaning "Be careful of your behavior," was derived from the practice of publicans (pub keepers) who recorded the number of drinks in pints or quarts served to each customer. A publican "minded his p's and q's" if he didn't lose money, and a customer "minded his p's and q's" if he did not get drunk (Austin, 1985; Carson-Dewitt, 2003).

In the early 1800s, a powerful alcohol prohibition movement began in the United States. Many groups contributed to this movement, including the American Temperance Union and the Washingtonians. Joining them were Protestants, Catholics, and other religious organizations.

These political forces achieved many local and state bans on alcohol sales and consumption. After overcoming a pause in these efforts during the American Civil War, they eventually were influential enough to help pass the National Prohibition Act, which became the **18th Amendment** to the U.S. Constitution in 1920. This amendment did not ban alcohol consumption, but it did ban the sale and distribution of alcohol. The 18th Amendment failed to eliminate alcohol use. In many communities, the ban on the sale of alcohol was virtually ignored, and *bootleggers*, those who illegally transported alcohol in the United States, were often regarded as celebrities. In 1933, the **21st Amendment** repealed the 18th Amendment. Still, although the federal government no longer prohibits the sale of alcohol, some towns and counties remain "dry" to this day. One of the most famous dry counties is Moore County, Tennessee—ironically, the home of Jack Daniel's distillery, a well-known whiskey producer (Carson-Dewitt, 2003; Hall, 2010).

**18th Amendment**
Amendment to U.S. Constitution that banned the sale and distribution of alcohol

**21st Amendment**
Repealed the 18th Amendment

## STOP & CHECK

1. The _____ provided the first written evidence of alcoholic beverages.
2. Other than recreational use, what were the first spirits used for?
3. Which U.S. constitutional amendment prohibited the sale and distribution of alcohol?

1. Sumerians 2. Dating back to A.D. 1250, the first spirits were used as medicines. 3. the 18th Amendment

## Pharmacokinetic Factors and Alcohol's Effects

Alcohol is highly fat soluble, allowing for easy absorption in tissue. Nearly all users consume alcohol orally, and after ingestion alcohol absorbs into the bloodstream through the gastrointestinal tract. Some of the consumed alcohol absorbs in the bloodstream through the stomach, while most alcohol absorbs through the upper intestine due to its large surface area. In the intestine, alcohol also impairs thiamine transporter

function, also known as Vitamin B1, reducing thiamine availability for critical cellular functions in the body (Subramanya, Subramanian, & Said, 2010). Thiamine deficiency occurs in Wernicke-Korsakoff syndrome, discussed later in this chapter.

On occasion, we find reports of alternative administration routes for alcohol, including intraocular, rectal, intravaginal, or inhalation methods. In general, users intend alternative forms to engender more rapid intoxication or, in a misguided attempt, to avoid calories from the oral route (Stogner, Eassey, Baldwin, & Miller, 2014). These routes bypass the first-pass effect, although the rectal administration route (colloquially referred to as an alcohol enema) still exposes alcohol to alcohol dehydrogenase enzymes in the rectum (Seitz et al., 1996). Overall, these alternative forms of alcohol administration are highly uncommon, with one study reporting non-oral consumption among 1.1 percent of surveyed alcohol users (Stogner et al., 2014).

We measure the amount of alcohol in the body by blood alcohol concentration. **Blood alcohol concentration** (or **BAC**) refers to the number of grams of alcohol in a 100 ml volume of blood. For example, 1 gram of alcohol in 100 ml of blood equates to a BAC of 1.0. This is an extremely high and fatal concentration of alcohol. A drink or two may produce a BAC of only 0.04. The maximum BAC from an alcoholic drink occurs after approximately 45 minutes (Dubowski, 1985).

**Blood alcohol concentration (BAC)**
Number of grams of alcohol in a 100 ml volume of blood

Enzymes in the stomach, liver, and other parts of the body metabolize alcohol. Given alcohol's oral administration route, we find alcohol undergoing first-pass metabolism, although little alcohol appears to be eliminated through its first pass through the liver (Weathermon & Crabb, 1999). Ninety-five percent of alcohol is converted by the enzyme **alcohol dehydrogenase**. Most of the remaining portion of alcohol metabolism comes from the P450 enzyme CYP2E1, although other cytochrome enzymes have been shown to metabolize alcohol as well. Alcohol dehydrogenase and CYP2E1 enzymes convert alcohol to **acetaldehyde**, a chemical that produces noxious effects (Zimatkin, Liopo, & Deitrich, 1998). CYP2E1 accounts for relatively little alcohol metabolism among infrequent drinkers; however, among chronic, heavy drinkers, CYP2E1 enzymes account for significantly more of alcohol's conversion to acetaldehyde (Lieber, 1997). Acetaldehyde converts to acetic acid and acetate by different forms of the enzyme aldehyde dehydrogenase, referred to as type 1 and type 2 (Chinnawirotpisan et al., 2003). Type 1 of aldehyde dehydrogenase breaks down high concentrations of acetaldehyde, occurring after an episode of heavy drinking, whereas type 2 breaks down low concentrations of acetaldehyde, occurring after moderate drinking. The breakdown of acetaldehyde can also occur by the CYP2E1 enzyme. Another process converts acetic acid and acetate to carbon dioxide and water (**Figure 9.2**).

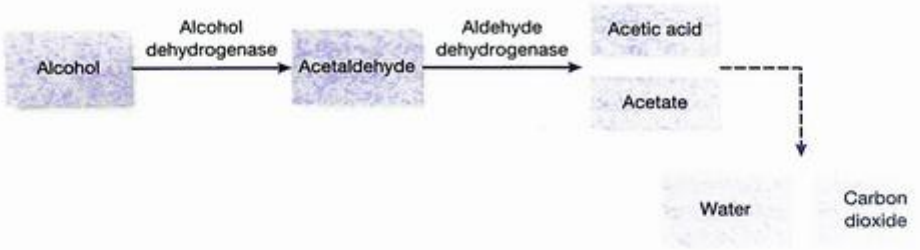
**Alcohol dehydrogenase**
Enzyme that metabolizes alcohol

**Acetaldehyde**
Metabolite produced from enzymatic conversion of alcohol with alcohol dehydrogenase

Both the stomach and liver contain alcohol dehydrogenase enzymes. Little alcohol first-pass metabolism takes place in an empty stomach, since alcohol quickly reaches the intestines in the absence of food. On a full stomach, however, alcohol remains in the stomach longer, giving alcohol greater exposure to alcohol dehydrogenase enzymes. In this case, some of the alcohol metabolizes before reaching the intestines for absorption. We also find differences in the rate of metabolism in the stomach between men and women. Twenty percent less first-pass metabolism of alcohol in the stomach occurs in women (Frezza et al., 1990). After absorption, alcohol dehydrogenase enzymes in the liver metabolize most of the remaining alcohol.

**FIGURE 9.2 Biotransformation of Alcohol**

The metabolic process for alcohol consists of conversion to acetaldehyde and then conversion of acetaldehyde to acetic acid and acetate. The other metabolic process causes acetic acid and acetate to convert to water and carbon dioxide.




Researchers have found different polymorphisms that affect the rate of alcohol metabolism. Those with the *alcohol dehydrogenase 1C*1 allele* polymorphism more quickly convert alcohol to acetaldehyde, leading to greater accumulation of acetaldehyde compared to those without this polymorphism (Coutelle et al., 2004). The *acetaldehyde H2*2 allele* polymorphism, which is found in approximately half of those of Asian descent, also causes a greater accumulation of acetaldehyde, but does so via slower catabolism of acetaldehyde by aldehyde dehydrogenase (Wall et al., 1997). This occurs due to less activity of type 2 aldehyde dehydrogenase, leading to a buildup of acetaldehyde until levels become high enough for type 1 aldehyde dehydrogenase to become active. The accumulation of acetaldehyde leads to facial flushing and nausea (Weathermon & Crabb, 1999).

As described in Chapter 4, the rate of alcohol elimination follows zero-order kinetics. Most individuals eliminate approximately 10 to 14 ml, or about ½ ounce, of 100 percent alcohol per hour. The general concept for alcohol elimination indicates that this elimination rate remains the same regardless of the amount of alcohol consumed. However, a truer picture of alcohol elimination presents a mix of zero-order and first-order kinetics, depending on the dose of alcohol ingested and the amount of enzymes available for metabolizing alcohol. Zero-order kinetics apply to alcohol's elimination rate until all available enzymes for metabolizing alcohol become saturated or completely occupied. This can occur from attaining and maintaining high BACs. After saturating alcohol metabolic enzymes, the elimination rate of alcohol approximates reductions in half-lives, which resembles first-order kinetics (Dubowski, 1985).

**Review!** Zero-order kinetics refers to drug elimination rates that do not occur in half-lives (Chapter 4).

Although 95 percent of alcohol is metabolized, the body eliminates the remaining five percent of alcohol, unchanged, from the lungs. The ratio of alcohol concentration in expelled air to blood is 1:2,300 (Dubowski, 1985). *Breathalyzer tests* use this ratio to accurately determine the amount of alcohol in blood. The amounts of alcohol analyzed are expressed as BAC. For example, saying someone "blew a 0.11" means a BAC of 0.11. Researchers correlate BACs to alcohol's pharmacological effects, and law enforcement uses BACs to determine if someone is legally intoxicated.

## STOP & CHECK

1. The percentage of alcohol in blood is referred to as the _____.
2. The enzyme alcohol dehydrogenase converts alcohol to _____.
3. Because a set rate of 10 to 14 ml of alcohol are eliminated per hour, alcohol is eliminated following _____ kinetics.

1. blood alcohol concentration 2. acetaldehyde 3. zero-order

## Alcohol and Interactions With Other Drugs

Given the prevalent use of alcohol, its pharmacological actions and effects should be considered for interactions with other drugs. These interactions can include pharmacokinetic effects, which may affect metabolism of alcohol or the drug being taken, or pharmacodynamic effects, which will alter a drug's physiological, behavioral, or subjective effects. Over-the-counter and prescribed medications that have known interactions with alcohol note warnings about consuming alcohol.

Pharmacokinetic drug interactions with alcohol primarily consist of the activities of enzymes involved in alcohol metabolism (**Table 9.1**). As noted earlier, metabolism of alcohol primarily occurs via the alcohol dehydrogenase enzyme. Some drugs, like aspirin and stomach acid reducers, inhibit activity of alcohol dehydrogenase enzymes, resulting in less metabolism of alcohol. This effect may especially strengthen the effects experienced from alcohol since less alcohol breaks down during first-pass metabolism.

While alcohol dehydrogenase metabolizes most of the alcohol one consumes, other enzymes, including CYP2E1, also metabolize alcohol. We find this particular enzyme involved in the metabolism of certain drugs, and the rate of metabolism for a drug becomes factored in when determining the doses to be taken. In this case, alcohol engages CYP2E1 enzymes, which leaves fewer CYP2E1 enzymes available to break down medications that one may have taken while drinking. For example, CYP2E1 metabolizes acetaminophen, and if consuming alcohol, the divided population of CYP2E1 enzymes to break down either alcohol or acetaminophen ultimately results in slower metabolism of both drugs. This effect occurs for certain antibiotics

**TABLE 9.1 Alcohol and Drug Interactions**

| Type of Drug Interaction | Examples of Drugs |
|---|---|
| Drugs that inhibit alcohol dehydrogenase, reducing biotransformation of alcohol, including first-pass metabolism | Aspirin and stomach acid reducers |
| Reduction of gut bacteria that metabolize alcohol will maintain alcohol longer in the body in an unmetabolized form | Antibiotics |
| Metabolism of drugs occurring through CYP2E1, which is active during metabolism of alcohol and will slow metabolism of these drugs | Acetaminophen; some antibiotics and barbiturates |
| Drugs that inhibit aldehyde dehydrogenase, causing nausea and facial flushing | Chlorpropamide; certain antibiotics |
| Metabolic interactions leading to production of active metabolites | Cocaine (forms coca ethylene) |
| Enhanced sedative-hypnotic effects | Benzodiazepines, barbiturates, GHB, and opioids |
| Enhanced confusion, agitation, and euphoria | Muscle relaxers |

and barbiturates as well. Similar drug interactions may occur for other enzymes involved in the metabolism of alcohol.

Drug interactions can also affect metabolism of acetaldehyde, again produced by the enzymatic actions of alcohol dehydrogenase with alcohol. Acetaldehyde accumulation may occur from the inhibition of aldehyde dehydrogenase enzymes. Drugs that produce this effect include certain antibiotics and older treatments for diabetes, such as chlorpropamide. When this occurs, the accumulation of acetaldehyde produces facial flushing and nausea, similar to what may occur following heavy consumption of alcohol.

Drug interactions with alcohol can also lead to the production of active metabolites. As noted in Chapter 6, administration of alcohol and cocaine leads to the production of the active metabolite coca ethylene—a psychostimulant compound (Jatlow et al., 1991). Similarly, alcohol and the attention deficit hyperactivity disorder treatment methylphenidate lead to the production of the psychostimulant ethylphenidate (Markowitz et al., 2000).

Beyond the pharmacokinetic interactions with alcohol, drugs that exhibit similar pharmacological effects with alcohol will together lead to stronger effects. For example, drugs that exhibit hypnotic and sedative effects will lead to a strengthening of these effects with alcohol. This will occur with barbiturates, benzodiazepines, GHB, and opioids. For muscle relaxers, alcohol enhances mental confusion and feelings of euphoria.

## Alcohol and Central Nervous System Functioning

The pharmacological actions of alcohol in the body involve many different neurotransmitter systems and depend on the amount of alcohol consumed. These pharmacological actions involve GABA, glutamate, endogenous opioid, dopamine, serotonin, and endocannabinoid systems (**Table 9.2**).

### Alcohol and $GABA_A$ Receptors

Alcohol acts directly on ionotropic $GABA_A$ receptors, which produce inhibitory effects on neurons (Mihic et al., 1997). When GABA activates $GABA_A$ receptors, the associated channels open and cause negatively charged chloride ions to enter the neuron. Negatively charged ions in turn hyperpolarize the neuron, inhibiting the neuron's activity.

Alcohol binds to and functions as a positive modulator for $GABA_A$ receptors (Ticku, Burch, & Davis, 1983). It does so through binding to a specific allosteric site on the $GABA_A$ receptor, thusly named the *ethanol binding* site. Positive modulation of $GABA_A$ receptors increases the length of receptor activation and increases the flow of chloride ions into the neuron. These two actions enhance the inhibitory effects of $GABA_A$ receptors.

**Review!** Positive modulators facilitate neurotransmitter actions at a receptor (Chapter 4).

**TABLE 9.2 Alcohol's Pharmacological Actions**

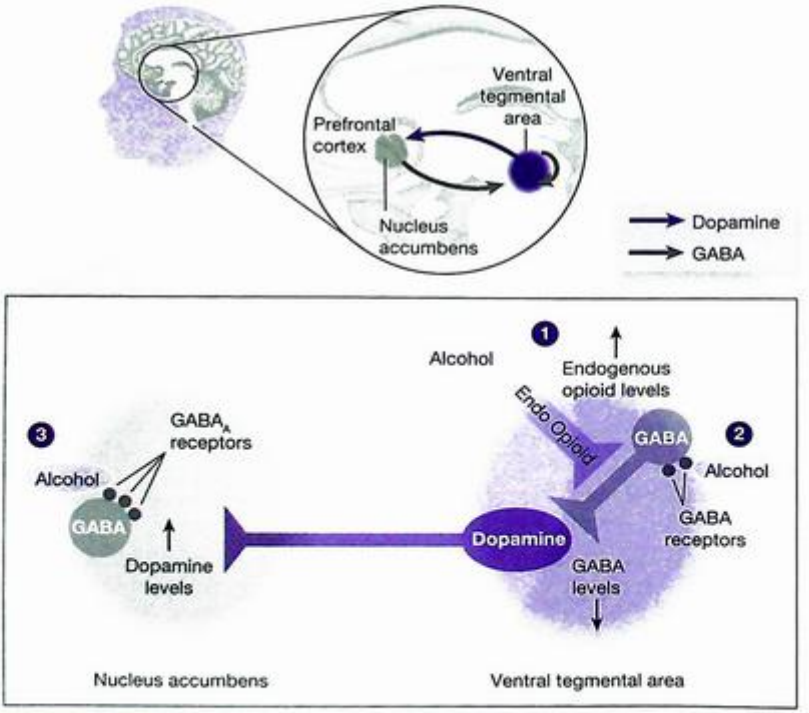
| Site | Actions |
|---|---|
| $GABA_A$ receptors | Positive modulator for $GABA_A$ receptors; inhibits activity in hippocampus, thalamus, and cerebral cortex for depressant effects. Exhibits rewarding effects in nucleus accumbens. |
| NMDA receptors | Noncompetitive antagonist for glutamate NMDA receptors, which counteracts excitatory effects otherwise resulting from glutamate neurotransmission. Contributes to rewarding effects in nucleus accumbens. |
| L-type calcium channels | Inhibits neurotransmitter release. Especially inhibits vasopressin release. |
| Increased brain serotonin levels | Leads to activation of $5\text{-}HT_3$ and $5\text{-}HT_{2A}$ receptors, which in turn contribute to increased dopamine levels in the nucleus accumbens. Other actions on the $5\text{-}HT_3$ and $5\text{-}HT_{2A}$ receptors described in the text. |
| Endocannabinoid receptors | Endocannabinoid $CB_1$ receptors mediate alcohol-induced elevations in nucleus accumbens dopamine levels. |

The location of $GABA_A$ receptors determines the effects of alcohol. Although many brain structures contain $GABA_A$ receptors, those most relevant to alcohol's CNS depressing effects include the cerebral cortex, hippocampus, and thalamus. These three structures are important for information processing, memory, and other cognitive activities.

$GABA_A$ receptors also mediate alcohol's reinforcing effects (**Figure 9.3**). First, alcohol facilitates $GABA_A$ receptor activation in the nucleus accumbens, a known receptor action that produces reinforcing effects. Second, alcohol activates $GABA_A$

**FIGURE 9.3 Effects of Alcohol on the Reward System**

Alcohol produces rewarding effects through GABA neurotransmission in three ways: (1) alcohol enhances endogenous opioid release (β-endorphin), which inhibits GABA neuron activity; (2) alcohol enhances the inhibitory effects of $GABA_A$ receptors on ventral tegmental GABA neurons, and these two mechanisms prevent GABA's inhibition of dopamine neurons and cause increased nucleus accumbens dopamine release; and (3) alcohol also produces rewarding effects by facilitating $GABA_A$ inhibition of GABA neurons in the nucleus accumbens.



receptors located on GABA neurons in the ventral tegmental area. The activation of these receptors causes reduced GABA release, in turn decreasing the inhibition of dopamine neurons (Xiao, Zhou, Li, & Ye, 2007). Reduced inhibition of dopamine neurons results in enhanced dopamine release in the nucleus accumbens, a known rewarding action (Yoshimoto, McBride, Lumeng, & Li, 1992).

In addition to acting on $GABA_A$ receptors in the ventral tegmental area, alcohol indirectly inhibits GABA neurons by increasing levels of the endogenous opioid β-endorphin (Schulz, Wüster, Duka, & Herz, 1980). In the ventral tegmental area, β-endorphin activates inhibitory opioid receptors on these GABA neurons, further contributing to diminished GABA release (Figure 9.3) (Xiao & Ye, 2008).

Chronic administration of alcohol causes several changes in alcohol's effects on GABA neurons. First, chronic administration reduces the number of $GABA_A$ receptors. Second, $GABA_A$ receptors become less affected by alcohol (Montpied et al., 1991). Third, alcohol produces a lower increase in β-endorphin levels, resulting in less inhibition of GABA neurons (Schulz et al., 1980). As noted later in this chapter, reduced levels of $GABA_A$ receptors contribute to dangerous withdrawal symptoms.

## Alcohol and Glutamate Receptors

Alcohol also produces depressant effects by inhibiting excitatory glutamate NMDA receptors. NMDA receptors produce excitatory effects and facilitate learning and memory processes. Like $GABA_A$ receptors, alcohol binds noncompetitively to NMDA receptors, but not at a clearly identified site (Krystal, Petrakis, Mason, Trevisan, & D'Souza, 2003). After binding to the receptor, alcohol inhibits ion passage through the NMDA receptor channel.

Chronic alcohol administration increases the number of NMDA receptors. During withdrawal from alcohol, the enhanced levels of NMDA receptors allow glutamate to exhibit greater excitatory effects on neurons. These greater excitatory effects, combined with lower $GABA_A$ receptor levels, increase the risk of seizures, a serious alcohol withdrawal symptom (Grant, Valverius, Hudspith, & Tabakoff, 1990; Hillbom, Pieninkeroinen, & Leone, 2003).

Enhanced NMDA receptor function may occur during chronic alcohol use. The enhanced activity occurs by interfering with a negative feedback loop, involving a type of potassium ($K^+$) channel called SK2, for the NMDA receptor. Chronic alcohol use inhibits the function of SK2 channels, which likely diminishes the effectiveness of negative feedback (Mulholland, Becker, Woodward, & Chandler, 2011).

## Alcohol and Calcium

Voltage-gated calcium channels facilitate neurotransmitter release and many other functions, including gene expression and enzyme regulation. Not only does the nervous system contain voltage-gated calcium channels, but so does the heart, smooth muscle, kidneys, and pancreas. There are six known types of voltage-gated calcium channels; these are classified by the letters L, N, P, Q, R, and T. Among these, alcohol inhibits the L-type calcium channel.

Because of the widespread expression of L-type calcium channels in the brain, alcohol's inhibitory actions through these channels cause generalized effects. Overall, acute administration of alcohol reduces neurotransmitter release from axon terminals containing these channels. However, alcohol inhibition of L-type calcium channels specifically inhibits vasopressin release. By inhibiting vasopressin levels, alcohol causes increased urination. In addition, diminished vasopressin activity impairs cognition, disrupts circadian rhythm, lowers blood pressure, and enhances aggression (Walter & Messing, 1999).

Calcium may also play a role in negative feedback pathways for NMDA receptors. As noted above, SK2 channels negatively affect the activity of NMDA receptors, and chronic alcohol use diminishes SK2 channel function. Calcium activates SK2 channels. In the hippocampus, calcium enters neurons through the R-type calcium channel, providing a source of calcium within neurons to activate SK2 channels, thereby facilitating negative feedback for NMDA receptors (Mulholland et al., 2011).

**Review!** Vasopressin is an antidiuretic hormone, meaning that it causes the kidneys to absorb more water from the bloodstream (Chapter 3).

## Alcohol and Serotonin

In addition to the other mechanisms described so far, alcohol also increases serotonin concentrations in the nucleus accumbens (Yoshimoto et al., 1992). As reviewed in Chapter 6, increased serotonin concentrations in the nucleus accumbens contribute to the rewarding effects of cocaine and amphetamine, suggesting that increased serotonin levels may contribute to alcohol's rewarding effects as well. Alcohol also appears to exhibit specific actions on serotonin ionotropic 5-$HT_3$ receptors and metabotropic 5-$HT_{2A}$ receptors.

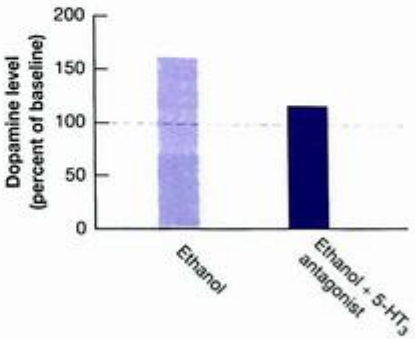
**Review!** An ionotropic receptor contains an ion channel, and a metabotropic receptor uses a G protein to carry out intracellular effects (Chapter 3).

Alcohol causes the activation of 5-$HT_3$ receptors through either of two ways. First, alcohol enhances serotonin levels, leading to greater activation of 5-$HT_3$ receptors. In the nucleus accumbens, for example, alcohol-induced increases in serotonin levels cause the activation of 5-$HT_3$ receptors, as well as any other serotonin receptors in the vicinity. Second, alcohol increases the flow of positively charged ions through the 5-$HT_3$ ion channel (Machu & Harris, 1994).

The involvement of 5-$HT_3$ receptors in alcohol-induced dopamine release can be assessed pharmacologically. Campbell and McBride (1995) used a microdialysis procedure in rats to assess alcohol administration with a 5-$HT_3$ receptor antagonist on dopamine release in the nucleus accumbens (**Figure 9.4**). In rats treated only with alcohol, dopamine levels significantly increased. Yet in rats administered the 5-$HT_3$ receptor antagonist ICS 205-930 into the nucleus accumbens, alcohol failed

**FIGURE 9.1** **Role of 5-HT$_3$ Receptor in Alcohol-Induced Dopamin Release**

The serotonin (5-HT$_3$) receptor antagonist ICS 205-930 prevented alcohol from increasing accumbens dopamine levels in rats, as indicated by the bar for the combination of ethanol the 5-HT$_3$ receptor antagonist being near the 100 percent mark. The y-axis refers to dopar levels as expressed as a percentage of baseline levels (i.e., 100 percent equals a baseline responding).




Source: Based on data from Campbell and McBride (1995).

to increase dopamine levels (Ding et al., 2011). These findings suggest th receptors may be important for alcohol's ability to increase dopamine conc in the nucleus accumbens.

Beyond serotonin receptors, the serotonin precursor tryptophan may a role in alcohol's effects, particularly in alcohol use disorders. Researchers fin blood plasma tryptophan levels in those with alcohol use disorders, inclu individuals are suffering from alcohol withdrawal symptoms. Tryptophan G protein-coupled receptor named GPR139, which may mediate some f addiction with alcohol. In a study by Kononoff and colleagues (2018), rats self-administer alcohol to the extent of becoming dependent upon it were gi that selectively served as an agonist for GPR139 receptors. The drug si reduced self-administration responses for alcohol. The authors suggested t ished tryptophan found in alcohol use disorder might lead to reduced ac these receptors. These findings may mean that reduced tryptophan levels to a failure to inhibit alcohol self-administration in alcohol use disorders (Ca

In addition to 5-HT$_3$ receptors, 5-HT$_{2A}$ receptors in the ventral tegm also contribute to alcohol's enhancement of nucleus accumbens dop els. As demonstrated in a study by Ding and colleagues (2009), the dire of a 5-HT$_{2A}$ receptor antagonist into the ventral tegmental are self-administration of alcohol in rats. The researchers attributed re administration to diminished dopamine release in the nucleus accumben

### Alcohol and the Endocannabinoid System

The endocannabinoid system may contribute to alcohol's reinforcing and other pharmacological effects. These interactions may depend partly on the role of the cannabinoid $CB_1$ receptor, which, as described in Chapter 11, influences the activity of dopamine neurons within the reward circuit. In a microdialysis study by Cohen, Perrault, Voltz, Steinberg, and Soubrie (2002), administration of the $CB_1$ receptor antagonist rimonabant prevented alcohol from increasing dopamine levels in the nucleus accumbens of rats. In another microdialysis study, alcohol failed to increase nucleus accumbens dopamine levels in $CB_1$ receptor knock-out mice (Hungund, Szakall, Adam, Basavarajappa, & Vadasz, 2003). Therefore, cannabinoid $CB_1$ receptors may be important for alcohol's ability to enhance nucleus accumbens dopamine levels.

## STOP & CHECK

1. Alcohol functions as a positive modulator for _____ receptors.
2. Alcohol inhibits ion passage through glutamate _____ receptors.
3. Alcohol's actions on L-type calcium channels have specific effects on the hormone _____.
4. Alcohol acts on the serotonin receptors 5-$HT_{2A}$ and _____.

1. GABA, 2. NMDA 3. vasopressin 4. 5-$HT_2$

## Pharmacological Effects of Alcohol

Alcohol's pharmacological effects vary, depending on alcohol's concentration in the body. In general, higher concentrations yield depressant effects on physiological and psychological functions, whereas lower concentrations yield excitatory effects for certain physiological and psychological functions. In addition, some of alcohol's effects change during chronic usage.

### Types of Drinking and Number of Drinks Consumed

Health officials apply certain terms to describe amounts of alcohol consumed. Studies use these terms to relate alcohol consumption to pharmacological effects. *Moderate drinking* consists of about two standard drinks per day for men and one standard drink per day for women (**Table 9.3**). By this definition, *light drinking* is less than these amounts. *Heavy drinking* consists of more than four drinks per day for men and three drinks per day for women (Dufour, 1999). Further, heavy drinking can also consist of at least 14 drinks per week for men and seven drinks per week for women. In 2014, an estimated 9.3 percent of men and 3.2 percent of women in the United States had reported recently engaging in heavy alcohol consumption (Center for Behavioral Health Statistics and Quality, 2014b).

**TABLE 9.3 Different Types of Drinking**

| Type of Drinking | Standard Drinks Consumed |
|---|---|
| Light drinking | Less than two drinks per day for men; less than one drink per day for women |
| Moderate drinking | Two drinks per day for men; one drink per day for women |
| Heavy drinking | At least four drinks per day for men; at least three drinks per day for women |
| Binge drinking | Drinking occurs in short time period consisting of at least five drinks per day for men and at least four drinks per day for women |
| Extreme drinking | Two or three times the number of drinks considered as binge drinking |

Heavy drinking during a short period of time is given the term **binge drinking**. It consists of drinking at least five standard drinks for men and four standard drinks for women during one occasion. This definition is also called the "5/4 rule," referring to the drink definitions for men and women, respectively (Wechsler et al., 2002). These sessions can achieve BACs of 0.08 and higher. We find more adults stating that they engage in binge-drinking sessions rather than in patterns of general heavy drinking (i.e., a session of drinking rather than days of heavy drinking in close succession). In one survey, an estimated 30.0 percent of men and 16.4 percent of women in the United States had reported recently engaged in binge alcohol drinking (Center for Behavioral Health Statistics and Quality, 2014b).

**Binge drinking**
Consumption of at least five standard drinks for men and four standard drinks for women during one occasion

**Extreme drinking** consists of consuming two to three times more alcohol than in binge drinking. It is not uncommon among young adults. In a survey conducted among freshmen after their first two weeks in college, White, Kraus and Swartzwelder (2006) found that nearly 30 percent of men and 10 percent of women had already engaged in extreme drinking.

**Extreme drinking**
Consuming two to three times more alcohol than in binge drinking

Extreme drinking is especially prominent during 21st-birthday celebrations in the United States. According to surveys conducted by Rutledge, Park, and Sher (2008), most individuals reported binge drinking at their 21st birthday. Approximately 12 percent engaged in a type of extreme drinking called "21 for 21," meaning drinking 21 drinks on their 21st birthday. The involvement in 21 for 21 was similar between men and women in this survey. The estimated BAC levels among these drinkers exceeded 0.26.

## Acute Alcohol Consumption and Cardiovascular and Respiratory Functioning

The physiological effects of light to moderate alcohol consumption primarily involve the respiratory and cardiovascular systems. Alcohol's respiratory effects depend on the concentration level. At lower alcohol concentrations, such as a BAC around 0.03, alcohol increases respiration. Beyond these concentrations, alcohol inhibits respiration, and this inhibition increases as the alcohol concentration increases. Respiratory inhibition is a key factor in alcohol poisoning.

Alcohol produces concentration-related effects on the cardiovascular system. Alcohol causes blood vessels to dilate, improving blood flow throughout the body. By increasing blood flow in the skin and extremities, alcohol provides feelings of warmth and contributes to a false but common belief that alcohol warms the body. In truth, the diversion of blood flow to the skin and extremities diminishes blood flow to core body organs. This actually makes the body colder (Oscar-Berman & Marinkovic, 2007).

Alcohol's cardiovascular effects at low alcohol concentrations can promote cardiovascular health. Some of these health benefits include a reduced risk of ischemia, stroke, and vascular-related dementias. The health benefits of daily low alcohol use result from four primary effects (see **Table 9.4**).

**Review!** Ischemia is a reduced blood supply, and it often results from constricted blood vessels (Chapter 2).

First, chronic light daily alcohol use increases high-density lipoprotein (HDL) levels, also referred to as "good cholesterol." HDLs reduce other cholesterols in the circulatory system. Second, chronic light daily use of alcohol reduces pro-inflammatory cellular signalling that contributes to the thickening of artery walls. Third, acute alcohol administration disrupts blood platelets from bonding together to form clots, the immediate cause of heart attacks and stroke. Fourth, acute alcohol administration causes blood clots to separate by causing the activation of *plasmin*, the enzyme responsible for degrading the bonding components between platelets in blood clots (Zakhari, 1997).

Although we find that light alcohol consumption provides health benefits for cardiovascular functioning, individuals with certain genetic traits may experience harm to the cardiovascular system from light consumption. For example, individuals with a polymorphism for the *alcohol dehydrogenase type 3 enzyme* may exhibit a reduced rate of alcohol metabolism and subsequently have an increased risk of heart attack associated with moderate alcohol consumption (Hines et al., 2001). In this regard, alcohol serves as an example of **hormesis**, beneficial effects produced by low doses of a toxic substance (Cook & Calabrese, 2006). Later in this chapter, we discuss adverse effects of alcohol that can occur even from moderate or light use.

**Hormesis**
Beneficial effects produced by low doses of a toxic substance

**TABLE 9.4 Effects of Light and Heavy Alcohol Consumption on Cardiovascular Health**

| Light Chronic Consumption (one to two drinks per day) | Heavy Chronic Consumption (several drinks per day) |
|---|---|
| Decreased risk of ischemia | Increased risk of ischemia |
| Decreased risk of heart disorders | Increased risk of heart disorders |
| Decreased risk of heart attack | Increased risk of heart attack |
| Decreased risk of stroke | Increased risk of stroke |

## Alcohol's Depressive Effects on Behavioral and Cognitive Functioning

Alcohol's depressant effects affect behavior and cognitive processing. Beginning at low BACs, alcohol impairs balance and equilibrium (**Figure 9.5**). Impaired equilibrium occurs at BACs as low as 0.05 (Liguori, D'Agostino, Dworkin, Edwards, & Robinson, 1999). This BAC falls below the legal limit for U.S. states, but it serves as the legal driving limit for many European countries. During field sobriety testing, which is conducted when a police officer suspects an individual is driving intoxicated, equilibrium is assessed by having an individual walk on a straight line, walk and then turn, or attempt to balance on one leg.

Alcohol use also causes poor judgment as a result of **disinhibition**, a weakening of behavioral control that manifests as poor risk assessment, engagement in dangerous behavior, and impulsivity. Disinhibition with alcohol use can cause socially unconventional behavior such as loud outbursts or aggressive behavior (Oscar-Berman & Marinkovic, 2007).

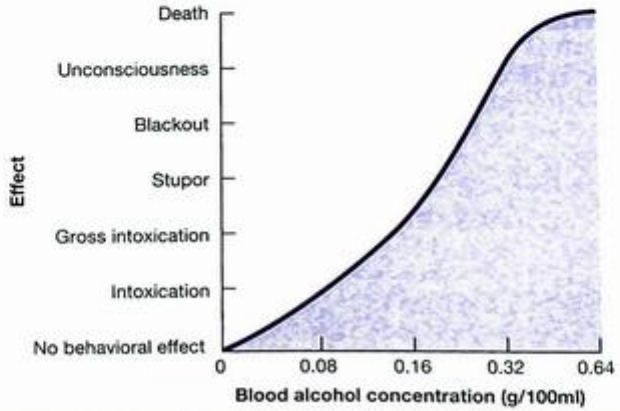
**Disinhibition**
Weakening of behavioral control

A specific disinhibition trait in alcohol use is **impulsivity**, or decision making without reflecting adequately on the consequences of those decisions. Researchers use delay-discounting designs to measure impulsivity. These procedures present a participant with a choice between an immediate small reward or a delayed larger reward. Both acutely alcohol-treated participants and former alcohol-addicted participants exhibit impulsivity deficits in such tasks (Bjork, Hommer, Grant, & Danube, 2004).

**Impulsivity**
Decision making without reflecting adequately on the consequences of those decisions

**FIGURE 9.5** Blood Alcohol Concentrations and Pharmacological Effects

Relationship between blood alcohol concentration (BAC, *x*-axis) and pharmacological effects. The legal limit for operating a motor vehicle in most states is 0.08.




Sources: Adapted from the Centers for Disease Control and Prevention (2011a), and Loyola Marymount University (2006).

**Alcohol myopia**
Alcohol-induced state of narrowed attention, perceptions, and thoughts to cues, emotional states, or specific sets of information

Researchers refer to another factor in alcohol-impaired decision making as *alcohol myopia*. **Alcohol myopia** consists of an alcohol-induced state of narrowed attention, perceptions, and thoughts to cues, emotional states, or specific sets of information. The term *myopia* refers to "short-sightedness," which characterizes the lack of due consideration to ideas beyond information most readily available or how one feels at the time. An individual experiencing alcohol myopia may become fixated on particular ideas or plans, potentially disregarding more prudent alternatives.

In this way, alcohol myopia may serve as a competing explanation to disinhibition to account for poor decision making while intoxicated. Or, disinhibition may instead serve as a feature of alcohol myopia. During alcohol myopia, one's emotional state at the time of consuming alcohol may become fixed in place. For example, a user may experience positive feelings if in a celebratory mood prior to drinking, whereas a user may experience negative feelings if in a depressed mood prior to drinking.

In a summary of studies on alcohol myopia, Shahram Heshmat listed seven effects observed during a state of alcohol myopia (Heshmat, 2016). One of these effects includes deficits in attention. In this regard, one may drive impaired because attention is focused on getting somewhere rather than one's self-assessment of the ability to drive safely while intoxicated. Another effect is aggressiveness, due potentially to one's particular emotional state, but also to easily becoming provoked by focusing on and reacting to cues deemed aggressive from another individual. These and other effects are listed in **Table 9.5**.

**Alcohol priming**
Tendency of users to develop an urge to consume more alcohol after having one or two drinks of alcohol

After consuming one or two drinks of alcohol, users develop an urge to consume more alcohol, a phenomenon described as **alcohol priming**. The phenomenon may be partly the result of alcohol's ability to disinhibit behavior and to increase impulsive decision making. Priming occurs in non-addicted alcohol users, irrespective of drinking patterns, as shown in **Figure 9.6** (Rose & Grunsell, 2008).

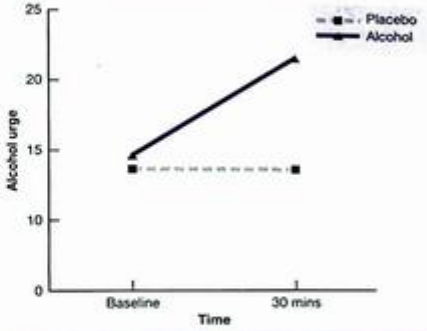
**TABLE 9.5 Effects of Alcohol Myopia**

| Effect | Description |
|---|---|
| Attention deficit | Attention shifts to motivations or cues most obvious and available |
| Impulsive behavior | Inability to consider risks of decisions that can lead to immediate rewards |
| Aggression | Increased level of provocation when confronted with aggressive cues |
| Overeating | Impaired monitoring of food intake due to focusing on immediate pleasures of eating without weighing consequences of greater food consumption |
| Self-awareness | Focus on cues and information around the individual shifts attention away from self-monitoring of behavior |
| Anxiety relief | Attention may shift from cues that serve as reminders of stress, thereby reducing anxiety |
| Empty promises | Commitments to plans based on desire to achieve a goal, but without due consideration to feasibility of reaching the goal |

*Source:* Based on Heshmat (2016).

**FIGURE 9.6 Alcohol Priming**

An urge to consume more alcohol occurred 30 minutes after consuming an alcoholic drink, as shown by the triangles. Baseline represents the urge to drink before consuming the first alcoholic drink. The *y*-axis represents the level of urge to consume alcohol with higher numbers corresponding to greater urges.




Source: Rose, A. K., & Grunsell, L. (2008). The subjective, rather than the disinhibiting, effects of alcohol are related to binge drinking. *Alcoholism: Clinical and Experimental Research, 32*(6), 1096–1104. doi:10.1111/j.1530-0277.2008.00672.x. Reproduced with permission of John Wiley & Sons Ltd.

Alcohol markedly reduces reaction time. These slower reaction times can occur at relatively low BACs and are especially dangerous when driving. Researchers use simulators to measure alcohol's effects on driving. In a study conducted by Liguori and colleagues (1999), placebo- and alcohol-treated participants operated a simulator to drive on a straight road at 50 miles per hour. During the simulation, yellow barricades appeared at random intervals, requiring participants to immediately press on the brake pedal. The reaction time consisted of the time between the presentation of the barricade and the pressing of the brake pedal.

**Figure 9.7** shows the results from this driving simulator study. Compared to placebo-treated participants, alcohol-treated participants reacted more slowly to the yellow barricades. These reaction deficits occurred for BACs as low as 0.05, and they were especially pronounced at a 0.08 BAC, a legal limit for operating motor vehicles in most states.

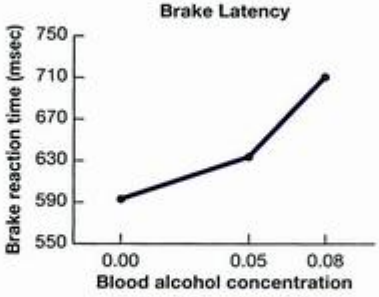
Reductions in reaction time extend to prenatally exposed infants as well. Jacobson, Jacobson, and Sokol (1994) tested the reaction time of infants from mothers who reportedly consumed small amounts of alcohol throughout their pregnancies. None of the infants were diagnosed with fetal alcohol syndrome. These infants exhibited significantly reduced reaction times compared to those whose mothers did not consume alcohol during pregnancy.

In addition to reaction time, alcohol significantly impairs **divided attention**, sustained attention on a stimulus despite the presence of distracters. Schulte, Müller-Oehring, Strasburger, Warzel, and Sabel (2001) demonstrated alcohol-associated deficits in divided attention. Using the grid shown in **Figure 9.8**, the researchers asked individuals to identify square patterns formed by X's in a rapid series of differently patterned screens. On this task, alcohol-treated participants who had a BAC of 0.05 or higher produced more errors than placebo-treated patients.

**Divided attention**
Sustained attention on a stimulus despite the presence of distracters

**FIGURE 9.7 Alcohol Impairs Braking Reaction Times**

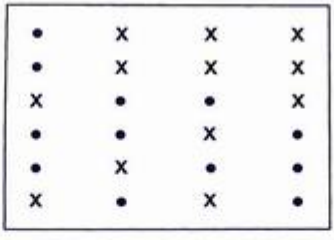
BACs as low as 0.05, shown on the *x*-axis, significantly impair brake reaction time (*y*-axis) in a driving simulator.




*Source:* Liguori, A., D'Agostino, R. B., Dworkin, S. I., Edwards, D., & Robinson, J. H. (1999). Alcohol effects on mood, equilibrium, and simulated driving. *Alcoholism: Clinical and Experimental Research, 23*(5), 815–821 doi:10.1111/j.1530-0277.1999.tb04188.x. Reproduced with permission of John Wiley & Sons Ltd.

**FIGURE 9.8 Divided Attention Task**

One type of divided attention task requires participants to identify square patterns with X's in an array such as this. Each array is shown only briefly.




*Source:* Adapted from Schulte, T., Müller-Oehring, E. M., Strasburger, H., Warzel, H., & Sabel, B. A. (2001). Acute effects of alcohol on divided and covert attention in men. *Psychopharmacology, 154*(1), 61–69.

Divided attention deficits, in particular, may help explain some of the characteristics of alcohol-related vehicle crashes. Johnston (1982) suggested that most crashes occur during obstructed road conditions such as maneuvering a vehicle around a tight curve. Such conditions rely on focused divided attention in order to successfully steer the vehicle amid a variety of road conditions.

**Vigilance**
A state of readiness for detecting and responding to unpredictable events

Alcohol does not affect all types of attention equally. Light to moderate alcohol consumption does not affect **vigilance**, a state of readiness for detecting and responding to unpredictable events. Nor does light to moderate alcohol consumption disrupt sustained attention, which is demonstrated by having someone focus intently on a single stimulus.

Alcohol produces deficits in memory, particularly at BACs of approximately 0.08 and higher. In a study of human volunteers with BACs of 0.04 and 0.08, those with BACs of 0.08 exhibited significant deficits in *episodic memory*, the conscious memory of a personally experienced event, and *semantic memory*, the memory of verbal or written information (Kleykamp, Griffiths, & Mintzer, 2010). However, BACs of 0.08 do not significantly affect working memory unless the working memory task is especially difficult (Grattan-Miscio & Vogel-Sprott, 2005; Gundersen, Specht, Grüner, Ersland, & Hugdahl, 2008; Kleykamp et al., 2010). Deficits in memory appear worse during inclining BACs than during declining BACs (Schweizer & Vogel-Sprott, 2008). Higher BACs may produce a complete inability to recall events while drinking, a phenomenon referred to as *blackout*, covered later in this chapter.

## Subjective Effects of Alcohol

After consuming alcohol, individuals usually report an improvement in mood. These effects increase as alcohol concentrations increase. Human study participants can detect clear drug effects at BACs of 0.05 consisting of a high and mild dizziness (Liguori et al., 1999). Alcohol users with BACs of 0.08 and higher report feelings of intense well-being. In general, alcohol produces a greater degree of stimulating effects when BACs are rising and a greater degree of sedating effects when BACs are falling (Martin, Earelywine, Musty, Perrine, & Swift, 1993).

Alcohol also produces relaxing effects, and many users consume alcohol to reduce feelings of stress. This appears to occur with lower amounts of alcohol, generally in conjunction with positive subjective effects (Brabant, Guarnieri, & Quertemont, 2014). In fact, Conger (1956) developed a **tension reduction hypothesis**, which holds that drinking alcohol reduces stress, to explain regular alcohol use. An important part of this hypothesis is that anxiety sufferers have a greater likelihood of drinking. Although this hypothesis is difficult to confirm in humans, animals identified with anxious traits have a greater likelihood to self-administer alcohol compared to non-anxious animals (Primeaux, Wilson, Bray, York, & Wilson, 2006; Spanagel et al., 1995). Moreover, stress and anxiety serve as predictors for alcohol addiction, as noted later in this chapter.

**Tension reduction hypothesis**
Drinking alcohol reduces stress

## STOP & CHECK

1. The game 21 for 21 is an example of _____ drinking.
2. How does alcohol produce feelings of warmth?
3. A specific disinhibitory effect of alcohol is _____, which can be measured using delay-discounting tasks.
4. Alcohol also impairs _____, which may explain why alcohol-related crashes occur during obstructed driving conditions.
5. Two key subjective effects of alcohol are an improvement in mood and a reduction in _____.

1. extreme 2. Alcohol dilates blood vessels, increasing blood flow to the skin and extremities. This provides a feeling of warmth. 3. impulsivity 4. divided attention 5. stress or anxiety

## Severe Adverse Effects of High BAC

**Alcohol stupor (or drunken stupor)**
Dulled senses and poor cognitive functioning caused by overconsumption of alcohol; also known as drunken stupor

**Reversible drug-induced dementia**
Reversible drug-induced dementia characterized by stupor and anterograde amnesia

**Blackout**
Term used to describe anterograde amnesia due to alcohol use

**En bloc blackout**
A total inability to recall events during a set period of time of alcohol intoxication

Acute alcohol consumption generates severe adverse effects above a 0.20 BAC (see Figure 9.5). At these BACs, drinkers develop an **alcohol stupor**, or **drunken stupor**, that is characterized by disorientation, dulled senses, and poor cognitive function. Someone described as *drunk*, *smashed*, or *hammered* exhibits many of the signs of stupor.

At BACs of 0.25 and higher, drinkers can develop a reversible drug-induced dementia. **Reversible drug-induced dementia** is characterized by stupor and anterograde amnesia, better known as **blackout.** Anterograde amnesia is the inability to form new memories. This type of dementia is called *reversible* because the effects subside as BAC levels decline (Oscar-Berman & Marinkovic, 2007).

Blackout from alcohol occurs as either of two types, *en bloc* or *fragmentary*. **En bloc blackout** consists of a total inability to recall events during a set period of time of alcohol intoxication. These blackouts reflect a disruption in converting short-term memories into long-term memories. This means that during the drinking session, the user maintains short-term memory function, allowing the person to carry on conversations and engage in other behaviors, but an ability to convert these experiences into long-term memory precludes any later recollection of those events. As indicated earlier, a high BAC, such as 0.25, is needed to produce the en bloc type of blackout (Rose & Grant, 2010).

Blackouts occur due to the effects of alcohol on neurotransmission for memory systems. In particular, the alcohol's noncompetitive antagonism of glutamate NMDA receptors (noted earlier) interferes with the process of long-term potentiation—a critical component for memory. The process relies on activation of NMDA receptors, and alcohol's inhibition of this process affects the formation of new memories. The effect that alcohol has on long-term potentiation in the hippocampus appears to impair long-term memory formation (Rose & Grant, 2010).

**Review!** The hippocampus mediates long-term memory formation and retrieval (Chapter 2).

**Fragmentary blackout (or brownout)**
Incomplete memories from a period of alcohol intoxication

**Alcohol poisoning**
Alcohol-induced inhibition of autonomic system functions, including breathing, heart functioning, and the gag reflex

**Fragmentary blackout** (sometimes referred to as a **brownout**) consists of incomplete memories from a period of alcohol intoxication. Prompting by others can make users aware of forgetting certain events from that period. Unlike en bloc blackouts, fragmentary blackouts can occur at lower BACs, even as low as 0.06 for some users. These blackouts might occur from impaired encoding for long-term memories, as opposed to the en bloc type (Rose & Grant, 2010).

At higher BACs, drinkers may pass out. Unconsciousness occurs when alcohol in the brain reaches sufficient concentrations to dampen cortical functioning and cortical arousal areas in the forebrain and brain stem. As BACs rise further, so does the inhibition of CNS functioning.

A particular risk of high BACs is the suppression of function in the hindbrain, which includes the medulla, a structure critical for autonomic processes such as breathing. BACs of approximately 0.25 and higher can cause **alcohol poisoning**, an alcohol-induced inhibition of autonomic system functions, including breathing, heart

functioning, and the gag reflex. During alcohol poisoning, most deaths occur from depressed respiration (Adinoff, Bone, & Linnoila, 1988).

Binge and extreme drinking carry a significant risk of alcohol poisoning. The number of drinks consumed during these forms of drinking reach these high BACs, yet the speed of alcohol consumption is the most critical determinant for alcohol poisoning. As stated previously, although users feel alcohol's effects within minutes, the maximum absorption of alcohol occurs after 30 minutes. This means that a quick succession of alcoholic drinks during a binge causes a dramatic increase in BAC levels.

## Chronic Alcohol Consumption and Adverse Cardiovascular and CNS Effects

Although chronic light alcohol consumption may provide positive benefits for the cardiovascular system, chronic exposure to alcohol, no matter the drinking level, can expose users to other risks. One of these risks, as discussed earlier, is *alcohol priming*, which increases the likelihood of consuming more alcohol than was originally intended. Another is cancer risk. Alcohol use is associated with increased rates of a variety of cancers, including cancers of the liver, gastrointestinal tract, and breast (Cogliano et al., 2011). Moreover, we also link the metabolic product from alcohol metabolism, acetaldehyde, with cancer risk, particularly for breast cancer. The risk increases for those with the alcohol dehydrogenase 1C*1 allele (ADH1C*1 allele) polymorphism, because these individuals more quickly convert alcohol to acetaldehyde and create greater levels of acetaldehyde compared to those without this polymorphism (Coutelle et al., 2004).

Chronic heavy alcohol consumption causes many negative effects: increased risks of ischemia, stroke, and heart attack. One of these adverse effects is cardiomyopathy, which consists of any number of specific disorders that affect the heart muscle. Chronic heavy alcohol use can cause **alcoholic cardiomyopathy**, which is characterized by low cardiac output because of enlargement of the heart and dilation of the heart chambers. This disorder leads to congestive heart failure, the inability to adequately supply blood to the body.

**Alcoholic cardiomyopathy**
Low cardiac output from enlargement of the heart and dilation of heart chambers caused by heavy and chronic alcohol use

Heavy acute or chronic alcohol consumption can cause *cardiac arrhythmias*, which are characterized by abnormal or rapid heartbeats. Cardiac arrhythmias that occur after an acute heavy drinking episode constitute what is referred to as a **holiday heart syndrome**. These effects range in severity and account for approximately five percent of alcohol-related deaths (Zakhari, 1997).

**Holiday heart syndrome**
Cardiac arrhythmias occurring after an acute heavy drinking episode

Unlike the dilating effects of light alcohol consumption, heavy alcohol consumption constricts blood vessels. This hypertensive state is particularly dangerous for individuals suffering from cardiomyopathy, because the ability to pump blood is already diminished. Hypertension requires increased heart output to deliver blood through the high-pressure system (Zakhari, 1997).

Repeated use of alcohol can lead to progressive stages of liver disease, beginning with fatty liver disease, and then inflammation, liver fibrosis, and finally liver cirrhosis. The term *alcoholic fatty liver disease* becomes applied if the condition coincides with regular moderate to heavy drinking. **Alcoholic fatty liver disease** consists of fat accumulation in the liver due to regular alcohol consumption. When

**Alcoholic fatty liver disease**
Fat accumulation in the liver due to regular alcohol consumption

unrelated to alcohol, but instead due to poor diet, obesity, insulin resistance, or other factors, the term *non-alcoholic fatty liver disease* is used instead. Fortunately, the conditions of alcoholic fatty liver disease recede following extensive abstinence from drinking.

Alcoholic fatty liver disease proceeds to inflammation of the liver and then damage to cells if heavy chronic drinking continues, leading to liver fibrosis. *Liver fibrosis* consists of scar tissue that diminishes liver function. An advanced stage of liver fibrosis is **cirrhosis**, a chronic liver disease characterized by poor liver functioning that includes tissue scarring and diminished blood flow through the liver. These conditions compromise the liver's ability to take in and metabolize nutrients from foods, synthesize proteins due to loss of metabolic enzymes, and carry out other vital processes (Lieber, 1997). Also due to reduced levels of metabolic enzymes, drug metabolism is diminished in cirrhosis, leading to long-lasting drug effects for many pharmacological substances (Elbekai, Korashy, & El-Kadi, 2004).

**Cirrhosis**
A chronic liver disease characterized by poor liver functioning due to tissue scarring and diminished blood flow, affecting nutrient metabolism, protein synthesis, and other vital processes

We also find heavy chronic alcohol consumption associated with pancreatitis, characterized by inflammation of the pancreas, tissue scarring, abdominal and back pain, nausea, and inhibited digestion. The pancreas releases enzymes important for digestion and hormones, including insulin. Damage occurs from the greater enzymatic activity involved in breaking down acetaldehyde, which occurs from regular acetaldehyde elevations from chronic heavy drinking (Nordback, MacGowan, Potter, & Cameron, 1991).

Alcohol use during pregnancy can cause **fetal alcohol syndrome**, a disorder characterized by physical and neurological abnormal development. Babies with fetal alcohol syndrome have characteristic facial abnormalities, such as a widened distance between the eyes, and risk of a variety of other physiological effects, such as congenital heart defects and abnormal development of the eyes and ears (**Figure 9.9**). These babies develop more slowly intellectually and cognitively and maintain deficiencies in these areas.

**Fetal alcohol syndrome**
Disorder characterized by physical and neurological abnormal development

The full onset of fetal alcohol syndrome is most associated with heavy alcohol use, particularly from pregnant mothers who engaged in binge drinking. Lesser amounts of alcohol consumed during pregnancy can produce a weaker fetal alcohol syndrome, referred to as *alcohol-related neurodevelopmental disorder*. A child born without the full spectrum of fetal alcohol disorder symptoms will have fewer physiological, behavior, and cognitive deficits (Sokol, Delaney-Black, & Nordstrom, 2003).

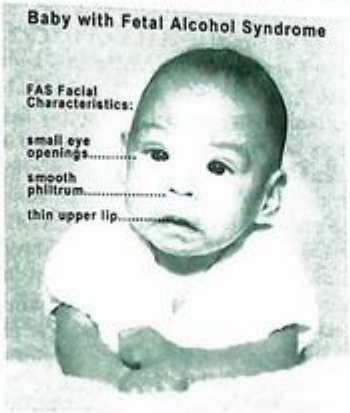
How much alcohol is safe to drink during pregnancy? The specific limit of alcohol consumption during pregnancy is a moving target. Most physicians recommend no consumption during pregnancy, whereas some advise only occasional consumption (Anderson et al., 2010). In 2005, U.S. Surgeon General Richard Carmona stated in an advisory on fetal alcohol syndrome risk that "it is now clear that no amount of alcohol can be considered safe [during pregnancy]" (Carmona, 2005). This remains the recommendation from the U.S. Surgeon General as well as the Centers for Disease Control and Prevention and the National Institute on Alcohol Abuse and Alcoholism.

Long-term, heavy use of alcohol may cause a serious central nervous system disorder called **Wernicke-Korsakoff syndrome**, a condition characterized

**Wernicke-Korsakoff syndrome**
Condition caused by heavy, long-term alcohol use resulting in memory loss, false memories, poor insight, apathy, and tremors

**FIGURE 9.9 Fetal Alcohol Syndrome**

Alcohol use during pregnancy can cause fetal alcohol syndrome, a disorder noted for physical facial abnormalities, as shown in the photograph, and other physical and neurological abnormalities.




*Source:* Courtesy of Teresa Kellerman.

by memory loss, false memories, poor insight, apathy, and tremors. We refer to false memories as part of *confabulation* when the individual confidently purports false memories without the intention to deceive. Coma can also occur in Wernicke-Korsakoff syndrome. This disorder manifests from the destruction of nervous system tissue resulting from thiamine, or vitamin B1, deficiency. Thiamine is deficient because alcohol inhibits thiamine absorption from the intestinal tract, as described previously (Kopelman, Thomson, Guerrini, & Marshall, 2009). A less severe form of Wernicke-Korsakoff syndrome is called *alcohol dementia*, which consists primarily of deficits in cognitive functioning (Moriyama, Mimura, Kato, & Kashima, 2006).

## STOP & CHECK

1. Chronic heavy alcohol use can produce _____, an enlargement of the heart and dilation of heart chambers.
2. Alcohol use during pregnancy can cause _____.
3. Chronic heavy alcohol use diminishes absorption of thiamine, which can cause a central nervous system disorder called _____.

1. alcoholic cardiomyopathy 2. fetal alcohol syndrome 3. Wernicke-Korsakoff syndrome

## Alcohol: Tolerance and Sensitization

**Acute tolerance to alcohol**
Tolerance that occurs when alcohol's behavioral effects are weaker for declining BACs than for inclining BACs

**Metabolic tolerance to alcohol**
Increase in liver alcohol dehydrogenase enzymes resulting in an increased rate of alcohol metabolism

**Pharmacodynamic tolerance to alcohol**
Reduced physiological responsiveness to alcohol's pharmacological actions

**Behavioral tolerance to alcohol**
Reduced behavioral impairment to alcohol

**Acute tolerance to alcohol** occurs when alcohol's behavioral effects are weaker for declining BACs than for inclining BACs. The term *acute tolerance* refers to the development of tolerance during the same session (Fillmore, Marczinski, & Bowman, 2005). The chart in **Figure 9.10** illustrates this condition.

In Figure 9.10, alcohol administration caused BACs to steadily increase until a maximum BAC of 0.12 was reached. Behavior was significantly impaired when BACs first reached 0.08. After the peak BAC, a BAC of 0.08 was again reached as BACs were declining later in the session. The second 0.08 BAC on the *declining* BAC curve, however, was less impairing than the first 0.08 BAC on the *inclining* BAC curve. In other words, tolerance developed to the effects of a 0.08 BAC.

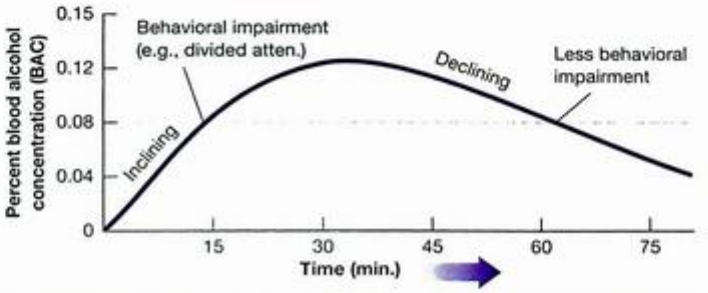
Other forms of tolerance develop through chronic administration. One of these forms is **metabolic tolerance to alcohol**, which consists of an increase in liver alcohol dehydrogenase enzymes and results in an increased rate of alcohol metabolism. The increased rate of alcohol metabolism diminishes BAC levels (Israel et al., 1979).

Another form of chronic tolerance is **pharmacodynamic tolerance to alcohol**, a reduced physiological responsiveness to alcohol's pharmacological actions. Pharmacodynamic tolerance is known to occur with glutamate NMDA receptors. As described previously, alcohol inhibits the function of NMDA receptors. During chronic administration, NMDA receptors are upregulated in order to compensate for alcohol's inhibitory actions at NMDA receptors (Gulya, Grant, Valverius, Hoffman, & Tabakoff, 1991).

Chronic alcohol administration also produces **behavioral tolerance to alcohol**, which is defined as a reduced behavioral impairment to alcohol. For example, Goodwin, Powell, and Stern (1971) demonstrated that experienced drinkers performed better on a simple motor task than novice drinkers after the administration of alcohol.

**FIGURE 9.10** Acute Tolerance to Alcohol

Acute tolerance occurs when behavioral impairment is less during declining BACs than during inclining BACs.



In addition to tolerance, sensitization occurs to some of alcohol's pharmacological effects. **Sensitization to alcohol** consists of an increase in alcohol's efficacy. In particular, sensitization occurs to alcohol's reinforcing effects. In animals, chronic alcohol administration produces an increase in alcohol self-administration, locomotor activity, and sexual behavior. Chronic alcohol administration also produces greater increases in dopamine levels in the nucleus accumbens compared to acute alcohol administration (for review, see Fish, DeBold, & Miczek, 2002).

**Sensitization to alcohol**
Increase in alcohol's efficacy, especially its reinforcing effects

## Alcohol Addiction and Withdrawal

Chronic heavy alcohol use often leads to an alcohol use disorder. Alcohol use disorder is generally synonymous with the term *alcoholism*, but alcoholism lacks the technical usage that an alcohol use disorder carries. An individual diagnosed with alcohol use disorder may meet all of the general DSM criteria for a substance use disorder as described in Chapter 5. In the United States, the lifetime prevalence of individuals exhibiting at least two of the eleven symptoms of an alcohol use disorder was found to be 29 percent (Grant et al., 2015).

Experts generally agree on two subtypes of alcohol addiction—type I and type II—although neither is included in the DSM-5 per se. The DSM-5 makes mention of environmental and genetic factors, but refrains from type I or type II designations. In 1987, Claude Cloninger first described the characteristics of these two types of alcohol addiction (Cloninger, 1987). Cloninger characterized **type I alcohol addiction** as occurring with those 25 and older and having low genetic risk but high psychosocial risk. Environmental variables such as stressful interpersonal situations or psychological disorders primarily account for type I alcohol addiction. Cloninger characterized **type II alcohol addiction** as occurring with those younger than 25 and exhibiting high genetic risk and traits associated with poor impulse control. Type II alcohol-addicted individuals often have a parent who was a chronic alcohol user, and they tend to engage in heavy drinking at a young adult age (**Table 9.6**).

**Type I alcohol addiction**
Alcohol addiction that occurs at age 25 or older, has low genetic risk, and exhibits high psychosocial risk

**Type II alcohol addiction**
Alcohol addiction that occurs before age 25, exhibits high genetic risk, and has traits associated with poor impulse control

A physiological dependence develops during alcohol addiction and leads to severe and potentially life-threatening withdrawal symptoms. *Seizures* are the primary withdrawal symptom of concern. Seizure risk develops as the brain adapts to alcohol's chronic actions in the brain. In particular, chronic alcohol use is associated with increased levels of glutamate NMDA receptors and decreased levels of $GABA_A$ receptors. The result of having more excitatory receptors and fewer inhibitory

**TABLE 9.6 Types of Alcohol Addiction**

| Types of Alcohol Addiction | Description |
|---|---|
| Type I | Occurs at age 25 and older; has low genetic risk and high psychosocial risk |
| Type II | Occurs at younger than age 25; has high genetic risk and poor impulse control |

receptors, respectively, is a hyperactivated state in many brain regions. This state sets the occasion for seizures. Because of this, anticonvulsant drugs should be provided during the first days of alcohol cessation therapy (Hall & Zador, 1997).

Repeated alcohol withdrawals, which may occur with someone who repeatedly quits and relapses, can increase the risk and severity of withdrawal seizures. An increased seizure risk from repeated withdrawals is called **kindling** (Ballenger & Post, 1978). Beyond seizure risk, alcohol withdrawal can produce an **alcohol withdrawal syndrome**, also referred to as **delirium tremens** (often called "DTs"), that is characterized by hallucinations, trembling, confusion, disorientation, and agitation (Hall & Zador, 1997).

**Kindling**
An increased seizure risk from repeated withdrawals from alcohol

**Alcohol withdrawal syndrome (delirium tremens)**
Alcohol withdrawal syndrome characterized by hallucinations, trembling, confusion, disorientation, and agitation

## STOP & CHECK

1. How is acute alcohol tolerance shown?
2. Between the two types of alcohol addiction, which has the greatest genetic risk?
3. Which alcohol withdrawal symptom is the greatest concern?

1. Acute alcohol tolerance is shown when declining BACs exhibit weaker effects than inclining BACs. 2. Type II alcohol addiction 3. seizures

## Treating Alcohol Addiction

A variety of therapeutic strategies exist for treating alcohol addiction. The ultimate goal of treatment is to eliminate the behavioral, social, and physical harm caused by alcohol use. To achieve this goal, most therapeutic approaches seek complete abstention from alcohol use. However, some therapeutic approaches seek to transform problem alcohol use into controllable alcohol use.

**Alcoholics Anonymous**
A 12-step program for alcohol addiction that provides extensive social support to encourage drinking abstinence for its anonymous members

**Cognitive-behavioral therapies for alcohol dependence**
Therapies that seek to improve an individual's cognitive and behavioral skills toward changing problem alcohol use

The 12-step recovery program **Alcoholics Anonymous** (AA) represents the most-recognized approach for alcohol addiction. Although numbers are difficult to determine because of the protected identities of participants, AA estimates it has 1.2 million members in the United States and 800,000 members elsewhere in the world (Alcoholics Anonymous, 2012). During AA meetings, a member shares personal stories about his or her struggles with alcohol use and connects with a sponsor who is normally a long-time AA member in recovery from alcohol addiction. AA programs provide extensive social support to encourage abstinence from drinking. Those who optimally respond to AA therapy have frequent meeting attendance, actively seek advice from AA sources, and strongly adhere to 12-step beliefs (Morgenstern, Kahler, Frey, & Labouvie, 1996).

**Cognitive-behavioral therapies for alcohol dependence** seek to improve an individual's cognitive and behavioral skills toward changing problem alcohol use. This approach views alcohol dependence as a maladaptive learning pattern that can be adjusted by replacing maladaptive responses with adaptive responses (Longabaugh & Morgenstern, 1999). These approaches have users learn to identify and cope with conditions that

facilitate problem alcohol use such as stress and alcohol-related stimuli (Witteman et al., 2015). By addressing alcohol use as maladaptive behavior, complete cessation of alcohol use is not the ultimate therapeutic goal per se. Rather, therapists seek to eliminate the problems associated with alcohol use, which may or may not require abstinence. These therapies are sometimes referred to as *controlled drinking therapies* because a user may learn to avoid excessive alcohol use and accompanying problems without completely abstaining from alcohol (Longabaugh & Morgenstern, 1999).

Pharmacological treatments for alcohol addiction attempt to reduce alcohol intake by (1) *producing aversive effects*, (2) *weakening effects*, or (3) *reducing cravings*. *Disulfiram (Antabuse)* has been used since 1949 to treat alcohol addiction and serves as the first compound used for chemical aversion therapy. **Chemical aversion therapy (or emetic therapy)** attempts to eliminate alcohol use by associating emesis (i.e., vomiting) with alcohol. Disulfiram discourages alcohol use by generating aversive effects through disrupting alcohol's metabolic process in the body. Disulfiram inhibits acetaldehyde dehydrogenase enzyme activity, the enzyme that breaks down acetaldehyde into inactive metabolites. After consuming alcohol, disulfiram, through inhibiting this enzyme, causes a buildup of acetaldehyde. Acetaldehyde, in turn, causes a number of adverse physiological effects, including nausea, sweatiness, and facial flushing (**Figure 9.11**). By producing these adverse effects, disulfiram may deter alcohol consumption (Heather, 1989).

**Chemical aversion therapy (or emetic therapy)**
Attempt to eliminate alcohol use by associating emesis (i.e., vomiting) with alcohol

Disulfiram appears most effective at reducing alcohol consumption when patients are willing to participate in cessation programs and when disulfiram compliance is supervised. Otherwise, alcohol-addicted individuals who are coerced, often through court-mandated treatment, into taking disulfiram either fail to take the medications regularly or switch to alternative drugs of abuse (Heather, 1989). Only one in five patients treated with disulfiram remains abstinent one year later (Miller, Walters, & Bennett, 2001).

**FIGURE 9.11 Pharmacokinetic Effects of Disulfiram**

Disulfiram inhibits the metabolism of acetaldehyde, causing acetaldehyde buildup and aversive effects after alcohol consumption.

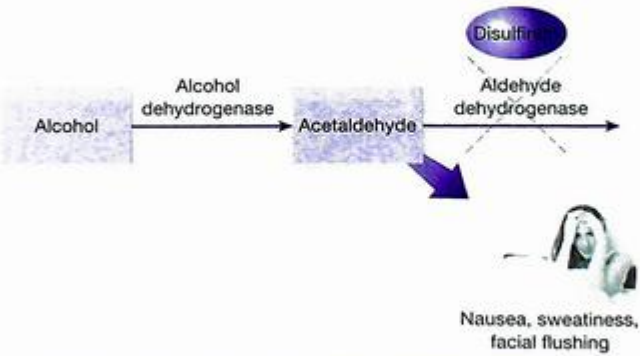



*Photo source:* Copyright iStockphoto/michaelpuche

Another aversion therapy approach specifically utilizes conditioned taste aversion procedures by having patients take a highly effective emetic substance (e.g., substance inducing nausea and vomiting) immediately after consuming an alcoholic beverage. For example, in a study by Elkins and colleagues (2017), in-house patients seeking treatment for alcohol use disorder agreed to undergo a procedure involving taking the emetic emetine, which induces nausea and vomiting, immediately after taking each of several types of alcoholic drinks. The process continued every other day for 10 days, and then the discharged patients returned one month and three months later for additional conditioning trials. One year later, sobriety was found among 69 percent of the 13 participants. The study also conducted fMRI scans before conditioning and then again near the end of the conditioning regimen and found reduced occipital lobe activity in response to visual images associated with drinking due to the conditioning sessions.

## Drug Profile: disulfiram

| | |
|---|---|
| Brand name | *Antabuse* |
| Mechanism of action | Inhibits acetaldehyde dehydrogenase |
| Uses | Reduces alcohol consumption by producing a buildup of the noxious substance acetaldehyde |

Although disulfiram treatment generates aversive effects, naltrexone treatment may reduce alcohol's reinforcing effects. *Naltrexone* is an opioid receptor antagonist approved in Canada, Europe, and the United States for treating alcohol addiction. By blocking opioid receptors, naltrexone may interfere with endogenous opioid mediation of alcohol's reinforcing effects, as described previously in this chapter (Volpicelli, Sarin-Krishnan, & O'Malley, 2002).

## Drug Profile: naltrexone

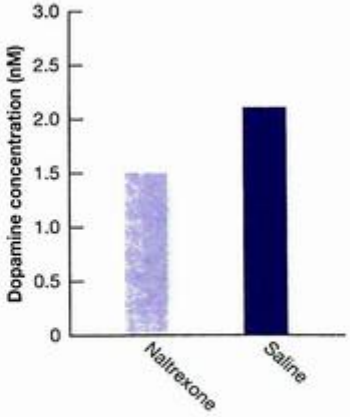
| | |
|---|---|
| Brand name | *Vivitrol, Revia, Depade* |
| Mechanism of action | Opioid receptor antagonist |
| Uses | Reduces reinforcing effects of alcohol by blocking contribution of endogenous opioids for alcohol-induced dopamine release in the nucleus accumbens |

Gonzales and Weiss (1998) demonstrated naltrexone's reduction of alcohol's reinforcing effects in rats using both self-administration and microdialysis procedures. In this study, rats self-administered less alcohol after naltrexone administration. Moreover, naltrexone caused a weaker elevation of nucleus accumbens dopamine levels after alcohol administration (**Figure 9.12**). In humans, naltrexone prevents alcohol-addicted individuals from consuming alcohol to dangerously high BACs (Volpicelli, Alterman, Hayashida, & O'Brien, 1992). Beyond this, however, naltrexone provides less than promising results for alcohol addiction. In a one-year clinical study conducted by Krystal, Cramer, Krol, Kirk, and Rosenheck (2001), naltrexone, in combination with psychosocial therapy, failed to increase the number of alcohol-free days compared to placebo.

*Acamprosate (Campral)* (the chemical name is *calcium*-bis[N-acetylhomotaurinate]) is a treatment approved by the Food and Drug Administration for alcohol addiction. Research suggests that acamprosate may treat alcohol addiction by reducing cravings for alcohol, although alcohol-induced reinstatement of craving appears unaffected (Littleton, 1995; Umhau et al., 2011). In clinical trials, acamprosate modestly reduces craving and increases the number of alcohol-abstinent days (Volpicelli et al., 2002). However, a collection of more recent studies has found that at six- and 12-month follow-ups with patients taking acamprosate, generally 20–40 percent of patients report alcohol abstinence (Mason, 2001).

**FIGURE 9.12** **Effects of the Opioid Receptor Antagonist Naltrexone on Alcohol-Induced Dopamine Release**

The opioid receptor antagonist naltrexone reduces alcohol's elevation of nucleus accumbens dopamine concentrations. The *y*-axis shows the amount of dopamine contained in each collected sample, as measured in nanomolar concentrations.




Source: Data from Gonzales and Weiss (1998).

For years, we considered acamprosate to engender these effects by acting on GABA and NMDA receptors. However, recent work by Spanagel and colleagues (2014) revealed that N-acetylhomotaurinate without calcium (i.e., they separated calcium from the acamprosate molecule) lacked any activity at NMDA or GABA receptors. This left one possible explanation for acamprosate's effect: calcium.

## Drug Profile: acamprosate

| | |
|---|---|
| Brand name | *Campral* |
| Mechanism of action | Calcium |
| Uses | May reduce risk of relapse by reducing activity of NMDA receptors |

As noted earlier in this chapter, alcohol inhibits calcium channels, preventing calcium from entering neurons. Calcium may provide a means for restoring negative feedback of NMDA receptors. In this way, calcium might contribute to reducing relapse by counteracting the increased activity of NMDA receptors caused by chronic alcohol use (Mulholland et al., 2011). Looking further, Spanagel and colleagues (2014) sought to determine why some patients fare better with acamprosate while others do not. They found that greater calcium levels in blood plasma correlated with longer times before relapse and with more time spent abstinent from alcohol. In fact, calcium therapy, referred to as *Calmonose*, had been used successfully in the past to reduce alcohol relapse (O'Brien, 1964).

## STOP & CHECK

1. Among the psychotherapies for alcohol addiction, which approach may not have alcohol abstinence as a goal?
2. How does disulfiram cause aversive effects after alcohol consumption?

1. Cognitive-behavioral strategies seek to reduce maladaptive behavior associated with alcohol. These strategies may succeed in reducing such maladaptive behavior without alcohol abstinence. For this reason, these approaches are often referred to as *controlled drinking therapies*. 2. Disulfiram inhibits breakdown of the alcohol metabolite acetaldehyde, a noxious chemical.

**Hangover**
Unpleasant experiences that may occur after alcohol consumption

## From Actions to Effects: Hangover

**Hangover** is an unpleasant experience that occurs after alcohol consumption. Its symptoms include headache, a poor sense of overall well-being, diarrhea,

fatigue, and nausea. Headache is the most common symptom (Harburg, 1981) (**Figure 9.13**). There is no set limit of drinks that will trigger hangover symptoms. The risk of hangover varies from individual to individual because of such factors as alcohol tolerance, enzymatic breakdown, medication interactions, and overall physical health. Other factors are addressed in the following text (Prat, Adan, & Sanchez-Turet, 2009).

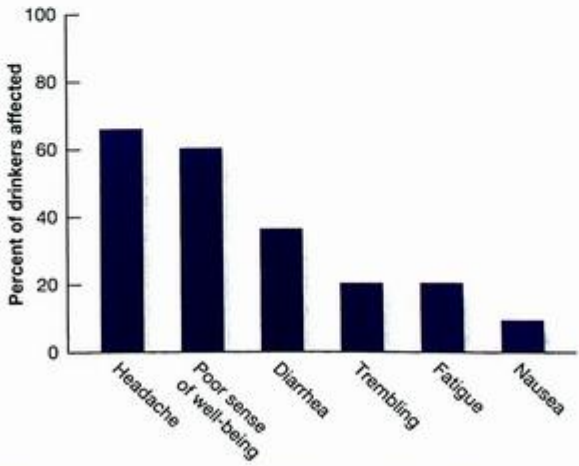
Hangovers not only are unpleasant but also are associated with cognitive deficits. These deficits occur even when BAC reaches zero. In a study by Howland and colleagues (2010), those experiencing hangover with no BAC levels exhibited significant deficits in reaction time and attention. The severity of the hangover relates to the magnitude of these deficits.

Hangover is highly prevalent in the general population. Based on survey information, nearly 75 percent of those drinking to intoxication have experienced a hangover, and about half of these drinkers experienced hangover within the last year. The prevalence of these debilitating effects present a high economic burden from worker absenteeism, low productivity, and accidents. Absenteeism, in particular, accounts for billions in lost wages each year (Wiese, Shlipak, & Browner, 2000).

Hangover symptoms appear around six to eight hours after drinking ceases. These symptoms begin to occur as the BAC approaches 0, and they worsen when

**FIGURE 9.13** **Hangover Symptoms Experienced by Drinkers**

Percentage of drinkers who have experienced types of hangover symptoms after an evening of drinking.




*Source:* Data from Harburg et al. (1981).

the BAC reaches 0. Once hangover symptoms occur, they remain for as long as 14–16 hours. The cause of hangover is not entirely understood. Currently, there are thought to be five possible contributors to hangover.

The first contributor to hangover may be acute alcohol withdrawal. Many of the features of hangover match the DSM characteristics for alcohol withdrawal. Moreover, alcohol consumption reduces hangover symptoms (Swift & Davidson, 1998). Unlike alcohol addiction, however, hangover symptoms do not develop into further stages of alcohol withdrawal such as seizures.

A second possible contributor to hangover is the buildup of acetaldehyde after alcohol consumption. As previously described, alcohol dehydrogenase converts alcohol to acetaldehyde. Acetaldehyde produces aversive hangover-like effects. However, alcohol consumption must be very high to produce sufficient buildup of acetaldehyde to produce aversive symptoms. Further, hangover symptoms occur when the body no longer contains acetaldehyde.

A third possible contributor to hangover may be acetate accumulation. A metabolite of acetaldehyde, acetate accumulates to much greater levels in the body than acetaldehyde and may be present in the body when hangover symptoms begin. Acetate causes other effects in the body, such as increased levels of adenosine, and causes headaches in humans and laboratory animals. Adenosine produces increased pain sensitivity and fatigue. Thus, acetate together with its production of adenosine may contribute to many hangover symptoms. In a demonstration of acetate's effects, Maxwell, Spangenberg, Hoek, Silberstein, and Oshinsky (2010) assessed the effects of acetate on headache in laboratory animals. The resulting headache from acetate was substantially reduced with treatment by caffeine, an adenosine receptor antagonist.

A fourth possible contributor to hangover is direct action by alcohol. Alcohol consumption causes dehydration, electrolyte imbalance, low blood sugar, vasodilation, and gastric irritation. All of these effects could support the symptoms of hangover. However, studies indicate that these specific effects are most related to *severe* hangover.

The fifth possible contributor to hangover is overconsumption of other chemicals in alcoholic drinks. These other chemicals can include acetones, polyphenols, and methanol. Methanol, in particular, is known to produce aversive effects similar to hangover. Moreover, hangover symptoms are worse for drinks with a high number of fermentation by-products, referred to as *congeners*, than those with less congener content. In a study conducted by Chapman (1970), more participants exhibited hangover after consuming bourbon, a drink with high congener content, than those who consumed vodka, a drink with low congener content.

Is there a treatment for hangover? All of the possible explanations for hangover just given are suggestive for potential treatment avenues. In practice, however, research addressing these explanations has yet to provide scientifically proven treatments. There still remains only one way to completely prevent hangover: Don't overindulge.

## STOP & CHECK

1. What is the most common hangover symptom?
2. Hangover symptoms worsen as the BAC approaches _____.
3. One of the possible explanations for hangover is that there is a buildup of _____, similar to how disulfiram reduces alcohol consumption.
4. Why might coffee reduce hangover symptoms?

1. headache 2. zero 3. acetaldehyde 4. Coffee contains caffeine, an adenosine receptor antagonist. Adenosine antagonism can counteract elevated adenosine levels, which cause elevated pain sensitivity and fatigue

## CHAPTER SUMMARY

Central nervous system depressants produce reinforcing and relaxing effects. By far the most used CNS depressant is alcohol, chemically known as *ethyl alcohol*. Although alcohol has been used for thousands of years, U.S. alcohol sales were prohibited during the 1920s.

Alcohol drink concentrations are measured as percentages or by proof, and we compare alcoholic drinks according to *standard drink* units. We also relate alcohol pharmacological effects to blood alcohol concentrations (BACs). Multiple steps occur for alcohol metabolism, and the alcohol elimination rate follows zero-order kinetics. Alcohol exhibits diverse pharmacological actions involving facilitation of GABA receptors, inhibition of NMDA receptors, activation of serotonin receptors, inhibition of calcium channels, and indirect actions involving endogenous opioids and endocannabinoids. These actions lead to reinforcing effects as well as impairing effects on cognition and behavior-reinforcing effects. Acute alcohol use can produce hangover, an overall sense of poor well-being marked by symptoms such as headache and nausea. Other adverse alcohol effects relate to long-term chronic usage, including damage to the heart and central nervous system. Several forms of tolerance develop for alcohol, and heavy chronic alcohol usage elicits severe withdrawal symptoms, including seizures. Alcohol is highly addictive and is addressed by both psychotherapeutic and pharmacological treatment strategies.

## KEY TERMS

Ethyl alcohol (or ethanol) 280
Methyl alcohol (or methanol) 280
Percentage alcohol (or alcohol by volume) 280
Proof of alcohol 280
Fermentation 280
Beer 281
Wine 281
Distilled alcoholic beverages 281
Standard drink 282
18th Amendment 284
21st Amendment 284
Blood alcohol concentration (BAC) 285
Alcohol dehydrogenase 285
Acetaldehyde 285
Binge drinking 295
Extreme drinking 295
Hormesis 296
Disinhibition 297
Impulsivity 297
Alcohol myopia 298
Alcohol priming 298
Divided attention 299
Vigilance 300
Tension reduction hypothesis 301
Alcohol stupor (or drunken stupor) 302
Reversible drug-induced dementia 302
Blackout 302
En bloc blackout 302
Fragmentary blackout (or brownout) 302
Alcohol poisoning 302
Alcoholic cardiomyopathy 303
Holiday heart syndrome 303
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CHAPTER 10

# Opioids

## Chapter Outline

- Opioids: Natural and Synthetic
- History of Opioid Use
- Pharmacokinetic Properties and Opioid Abuse
- Opioid Drugs and the Endogenous Opioid System
- Opioid Drugs Are Classified by Receptor Actions
- Opioids and Reward, Pain, and Stress Systems
- Opioid Rewarding and Analgesic Effects
- From Actions to Effects: Pharmacological Approaches for Treating Opioid Addiction

## Learning Objectives

- Describe the types and origins of opioids
- Examine the role of the endogenous opioid system for rewarding effects and pain relief
- Interpret the pharmacokinetic actions of opioids in the context of their manner and reasons for use
- Evaluate the effects of opioids and relate these effects to pharmacological actions

**Opioids**
Psychoactive substances that elicit pharmacological effects by acting on opioid receptors

**Narcotic**
A drug with sensory-dulling effects used to describe opioids but also non-opioid substances

**Opioids** consist of psychoactive substances that elicit pharmacological effects by acting on opioid receptors in the central nervous system (CNS) and other parts of the body. They are among the most effective pain-relieving medications today and among the most sought-after substances for abuse. The term **narcotic**,

from the Greek word narkōtikos, which means to "make numb," refers to sensory-dulling effects of a substance and is generally used by laypersons as a synonym for opioids. However, we find *narcotic* used to describe many other types of controlled substances, including psychostimulant drugs, such as cocaine. Thus, while the term *narcotic* is commonly used, it holds little value to scientists as a precise term.

Opioids serve as major drugs of abuse in the United States. The prevalence of opioid abuse occurs not only because of its rewarding effects but also because of its ease of access. We find increased opioid abuse in the United States, reaching levels that are now often referred to as an epidemic. Opioids commonly abused include not only heroin, but also synthetic opioid drugs. According to the most recent survey from the U.S. Department of Health and Human Services, an estimated 3,042,000 people in the United States reported recent illicit opioid use (Center for Behavioral Health Statistics and Quality, 2018). Deaths associated with opioids have dramatically increased through the 2000s. In the United States in 2001, approximately 9,400 deaths were reported due to opioid use, and the number increased to over 42,000 deaths in 2016 (Gomes et al., 2018).

Prescription opioid drugs such as *hydrocodone (Vicodin)* and *oxycodone (OxyContin)* are given to patients for the management of pain, but these drugs also have rewarding effects. Thus, a portion of adults might take these medications as directed, but then come to develop features of drug addiction. In an attempt to assess the risk of abuse from prescribed opioid drugs, Cicero, Ellis, Surratt, and Kurtz (2014) surveyed heroin users and found that 75 percent switched to using heroin after first using prescription opioids. Among these users, the reasons for switching to heroin not only included seeking a stronger high but also finding heroin more affordable than prescription opioids.

The known prevalence of users switching from a prescribed opioid to eventually an illicit opioid has placed a focus on how and why physicians prescribe these medications. While highly effective for pain, another non-opioid drug class for treating pain consists of *nonsteroidal anti-inflammatory analgesics*, such as acetaminophen (*Tylenol*) or ibuprofen (*Motrin*). These alternative drugs may be as effective for treating pain in many instances when an opioid analgesic was prescribed instead. In addition, non-pharmacological approaches to pain management might also be pursued, such as physical therapy.

Opioids may be more liberally prescribed than necessary. The leading perspective on why this has occurred consists of a published letter, the letter's influence on medical education, and aggressive promotion of opioid analgesics by pharmaceutical companies. In 1980, Jane Porter and Dr. Hershel Jick wrote a five-sentence letter to the *New England Journal of Medicine*—a journal widely read among physicians—stating that only four out of 11,882 patients developed a well-documented opioid addiction, according to their hospital's records (Porter & Jick, 1980). The finding was not alone in this claim, and by 1996, the American Pain Society and the American Academy of Pain Management issued a consensus statement that pain was undertreated and opioids seldom led to addiction among those without a previous history of addiction (American Academy of Pain Medicine and the American Pain Society, 1997).

During the 1990s, pharmaceutical companies extensively marketed their opioid medications, citing evidence that pain is undertreated and that a low addiction

risk accompanied these medications. The culmination of high prevalence of opioid addiction in the 2000s and 2010s and a re-examination of claims about the purported non-addictiveness of opioids has led to extensive lawsuits filed against pharmaceutical companies and distributors. In 2019, a number of opioid manufacturers agreed to multimillion- or multibillion-dollar settlements for class action lawsuits alleging that manufacturers engaged in false marketing that underplayed risks (Lopez, 2019). In 2017, the *New England Journal of Medicine*—40 years after publishing the letter by Porter and Jick—created a note above the 1980 article for when the article is retrieved electronically. The note states that the letter has been frequently cited but seldom given a critical review (McCook, 2017).

Beyond prescription opioids, another source of opioids comes from cough syrups. A prescription form of cough syrup includes codeine, which is highly effective for suppressing cough. Codeine is a schedule V substance in the United States. An over-the-counter opioid ingredient common in cough syrups is *dextromethorphan*. Dextromethorphan represents the "DM" in the brand-name cough syrup *Robitussin DM*. The slang term *robo-tripping* refers to psychedelic drug effects potentially achieved from drinking large quantities of cough syrups for recreational opioid use. High doses of dextromethorphan exhibit psychedelic effects (more on this substance in Chapter 12).

## Opioids: Natural and Synthetic

There are two main types of opioid compounds: those produced naturally and those produced through chemical synthesis in a laboratory. Natural opioids are found in opium exudate from the poppy plant *Papaver somniferum*. *Papaver somniferum* is an annual flowering plant that stands three to four feet high and has a vibrant pink, red, white, or violet flower (**Figure 10.1**).

**FIGURE 10.1** ***Papaver somniferum***

*Papaver somniferum* is an annual flowering plant that reveals an opium-containing seedpod after its petals fall off.

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A large seedpod, as shown in Figure 10.1, is revealed after the flower petals fall off only two to four days after flowering. After scoring the pod with a knife, a white substance emerges that turns red when exposed to air. This reddish resin is raw opium, and opium scraped from the seedpod can be used as is or further refined and processed, as described later in the chapter (Booth, 1998). Most opium cultivation occurs in Afghanistan, and it also occurs in Pakistan, Myanmar, Colombia, and Mexico (United Nations Office of Drugs and Crime, 2010).

**Naturally occurring opioid**
Opioid found in opium

We refer to opioids found within opium as **naturally occurring opioids**. The primary naturally occurring opioids are morphine and codeine (Wu & Wittick, 1977). The U.S. Drug Enforcement Administration (DEA) categorizes morphine and codeine as controlled substances, but they are not schedule I substances because of their legitimate medical uses. Morphine is a schedule II drug and is only available in hospitals, and codeine is a schedule III or IV product, depending on the quantity, and is used in prescription cough suppressants (Drug Enforcement Administration, 2012b) (**Table 10.1**). *Thebaine* is another component of opium but is a relatively minor component (Wu & Wittick, 1977).

While naturally occurring opioids, as a category, derive from opium, we find compounds that act on opioid receptors in other plants as well. Such plants are often noted for medicinal properties and exhibit features of opioid-like effects along with others, such as stimulant effects. One such plant is *Mitragyna speciose*, more commonly referred to as Kratom, Kakuam, and other names. The plant's primary psychoactive compound is mitragynine, which acts on opioid receptors. We find Kratom as a controlled substance in many countries and currently under review as a controlled substance in the United States.

**TABLE 10.1 DEA Schedules for Selected Opioids**

| Drug | Schedule |
|---|---|
| Buprenorphine | III |
| Codeine for cough syrup preparations | V |
| Diacetylmorphine (heroin) | I |
| Desomorphine | I |
| Fentanyl | II |
| Fentanyl synthetic analogs | I |
| Hydrocodone | II |
| Ketobemidone | I |
| Morphine | II |
| Methadone | II |
| Opium extract | II |
| Thebaine | II |

All other opioids are synthetically produced (**Table 10.2**). **Semisynthetic opioids** are synthesized from morphine or codeine. Semisynthetic opioids include *diacetylmorphine (heroin)*, *desomorphine (krokodil)*, *buprenorphine (Subutex)*, *hydrocodone*, *oxycodone (OxyContin)*, and many others. *Percocet* is a combination of oxycodone and *acetaminophen* (*Tylenol*), and *Vicodin* is a combination of hydrocodone and acetaminophen. Acetaminophen is not an opioid drug; instead, acetaminophen is a *nonsteroidal anti-inflammatory drug* (or NSAID for short) used for pain relief, which may result from reduced inflammation. Other NSAIDs include aspirin and *ibuprofen (Motrin)*.

**Semisynthetic opioids**
Opioid drugs synthesized from morphine or codeine

## Drug Profile: oxycodone + acetaminophen

| | |
|---|---|
| Brand name | *Percocet* |
| Properties | Oxycodone acts as an opioid analgesic, and acetaminophen acts as a *nonsteroidal anti-inflammatory drug* |
| Uses | Reduces pain by acting on opioid receptors and reducing inflammation |

**TABLE 10.2** **Selected Opioids and Their Types**

| | |
|---|---|
| Naturally occurring | Morphine |
| | Codeine |
| Semisynthetic | Buprenorphine (*Subutex*) |
| | Diacetylmorphine (*heroin*) |
| | Hydrocodone (*Vicodin*) |
| | Oxycodone (*Oxycontin*) |
| | Hydromorphone (*Dilaudid*) |
| | Oxymorphone (*Opana*) |
| Synthetic | Fentanyl (*Duragesic*) |
| | Dextropropoxyphene (*Darvocet-N*) |
| | Ketobemidone (*Cliradon*) |
| | Levacetylmethadol (INN) |
| | Methadone (*Dolophine*) |
| | Tramadol (*ConZip*, *Ultram*) |
| Novel synthetic opioids | U-47700 |
| | AH-7921 |
| | MT-45 |
| | W-18 |

Desomorphine, which goes by the street name *krokodil* (Russian for "crocodile"), is still a popularly abused opioid in Russia, despite harmful by-products made during its synthesis from codeine that cause severe toxicity to skin, muscle, and other tissues, particularly near injection sites. The by-products have given krokodil a reputation as a flesh-eating drug, which is not technically true (i.e., it's from toxic damage from chemical by-products) but the description serves well to describe the physical appearance of long-term krokodil users nonetheless (Grund, Latypov, & Harris, 2013).

**Synthetic opioids (or fully synthetic opioids)**
Opioids not derived from morphine, codeine, or any other naturally occurring opioid

The **synthetic opioids** (or **fully synthetic opioids)** are not derived from morphine, codeine, or any other naturally occurring opioids. Fully synthetic opioids include *fentanyl (Duragesic)*, *methadone (Dolophine)*, *ketobemidone (Cliradon)*, *levacetylmethadol (LAAM)*, and *tramadol (ConZip)*, among others. Fentanyl or known analogs of fentanyl, such as carfentanil, acetylfentanyl, and furanylfentanyl, serves as one of the most common synthetic opioids for abuse. Fentanyl or its analogs have been reported as the cause of opioid overdose death in more than half of cases in several areas of the United States, including Wayne County, Michigan (Detroit and greater Detroit area); Philadelphia, Pennsylvania; New York City, New York; and the state of Maine (National Drug Early Warning System, 2018). Overall, synthetic opioids account for most opioid overdose deaths in the United States (Jones, Einstein, & Compton, 2018).

While similar in structure to codeine and morphine, tramadol tends not to produce certain adverse effects, such as respiratory depression, common among opioids. Tramadol produces a relatively weak affinity for opioid receptors, and opioid effects from tramadol primarily come from its active metabolite, referred to as M1. Tramadol also occurs as a racemate, and between its enantiomers, (+)-tramadol appears the most active at opioid receptors and for enhancing serotonin reuptake, whereas (-)-tramadol inhibits reuptake of norepinephrine. Thus, while tramadol is classified as an opioid, the drug's analgesic effects derive from multiple pharmacological actions (Grond & Sablotzki, 2004).

The term *synthetic opioid* generally applies to compounds developed for the intention of providing new medications for the treatment of pain. Other synthetic opioids, however, are synthesized by clandestine laboratories for the purpose of developing an opioid drug not listed as a controlled substance. In these instances, researchers use the term *novel synthetic opioids*.

Many of these novel synthetics are derived from fentanyl, and if referring to another novel synthetic, the term *non-fentanyl derived novel synthetic opioid* is used instead. Non-fentanyl derived compounds tend to receive in-house laboratory identifications, such as U-47700 or AH-7921, since they were originally developed by pharmaceutical companies as either research compounds or potential therapeutic compounds that were abandoned early during development. For example, "U" in U-47700 refers to the Upjohn Company, and "AH" refers to the A.H. Robins Company. Clandestine chemists scour scientific reports for such compounds and attempt to synthesize them for abuse purposes (Solimini, Pichini, Pacifici, Busardò, & Giorgetti, 2018).

Naturally occurring opioids and synthetic opioids were developed for medicinal purposes. However, many opioids such as heroin offer powerful reinforcing effects,

precluding their medical use because of their addiction risk. Producers illegally synthesize heroin from morphine through a process that begins with extracting morphine from opium and then applying industrial chemical agents to synthesize heroin. After synthesis, heroin is packed and illegally shipped throughout the world (Hosztafi, 2001).

## STOP & CHECK

1. Why are opioid drugs easy to access?
2. What are the two primary opioids in poppy plants?
3. Morphine is used in the clandestine production of _____, a commonly abused opioid drug.

1. Although known illicit drugs such as heroin remain available, many users abuse prescription and over-the-counter medications that contain opioids. 2. morphine and codeine 3. heroin

## History of Opioid Use

Opium has been used since prehistoric times. Archeological research revealed evidence of *Papaver somniferum* plants in Neolithic villages in Switzerland. Historical records indicate opium cultivation in Egypt and Asia Minor in 3000 B.C., and ancient medical texts throughout Europe, the Middle East, and northern Africa list numerous medical uses for opium. Greek physician Hippocrates (460–357 B.C.) detailed the sleep-inducing and pain-relieving effects of opium and dismissed the magical interpretation of these effects by priests. Theophrastus (371–287 B.C.), a philosopher, referred to poppy juices as *opion*, which is now translated as *opium* (Duarte, 2005).

Soon after Rome conquered Greece, opium became intertwined with Roman culture and was purported as a treatment for a virtually endless list of maladies, including deafness, poisoning, and leprosy. The Romans regarded the poppy plant as a symbol of pain and death and regarded it as a convenient lethal poison. Arabs during this time cultivated and sold opium as a trading commodity. Moreover, they advanced the medical study of opium. Arab physician Avicenna (A.D. 980–1037) medically used opium for dysentery, diarrhea, and eye diseases as part of his 14-volume *Canon of Medicine*.

In the 16th century, Europeans developed and popularized a number of opium-containing medical potions, including **laudanum**. In the 1660s, English physician Thomas Sydenham developed the most common variety of laudanum. In this version, Sydenham made a drink containing opium, cinnamon, saffron, and fortified wine from the Canary Islands.

**Laudanum**
An opium-containing drink intended for medical purposes

During the 19th century, drug stores legally sold opium products such as morphine. In addition to selling morphine or another opioid as is, various elixirs for treating illnesses and pain contained morphine. Near the end of the 19th century,

the addictive effects of opioids received greater focus, and the beginning of the 20th century marks the religious and political movements leading up to the Harrison Act of 1914 (Booth, 1998; Duarte, 2005).

The Harrison Act did not directly ban opioid use, but rather limited the prescribing and sale of opioids to medical uses. Law enforcement interpreted this law as a means to prevent physicians from prescribing opioids to reduce opioid withdrawal symptoms. The enforcement of this law triggered an epidemic of addicted individuals leading to, according to a New York medical journal editorial on May 15, 1915, "crimes of violence . . . due usually to desperate effects by addicts to obtain drugs, but occasionally to a delirious state induced by sudden withdrawal" (Brecher, 1972, p. 50). Many other controlled substances acts followed. Today, opioids are among the most highly regulated medicines.

The terminology for opioids has changed over the years. Originally, the term *opiate* referred only to opium-derived compounds, and the term *opioids* referred to other opioid drugs. For example, under this distinction, morphine is an *opiate*, whereas heroin is an *opioid* (Steinberg & Sykes, 1985). However, these conventions are seldom followed, and in general, the term *opioid* describes all types of opioid and opiate compounds, and less often vice versa. Thus, *opioid* is the term used throughout this chapter. For researching material on opioids, one should use both terms in database searches to avoid missing any critical work.

## STOP & CHECK

1. What was the primary use of opium in ancient human history?
2. What was the first major U.S. law enacted to regulate opioid drug sales?

1. Opium was primarily used as a medicine in ancient history. Even though opioids are still used medicinally, their addictive properties have garnered much attention in modern history. 2. The Harrison Act of 1914

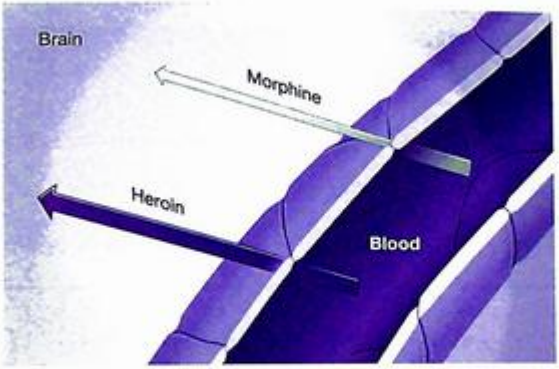
## Pharmacokinetic Properties and Opioid Abuse

In general, users administer opioids through inhalation, oral administration, or intravenous administration. The preferred routes of opioid administration depend on the particular drug and the purpose for using it. To achieve rewarding effects, users prefer intravenous injection or inhalation for a rapid speed of onset. The intravenous route also provides rapid relief from pain. Physicians prescribe codeine for oral administration to suppress coughing (Farré & Camí, 1991).

After absorption, opioids permeate the blood–brain barrier and enter the brain. Opioids differ in lipid solubility, affecting the time it takes them to reach the brain. For example, heroin crosses through the blood–brain barrier faster than morphine, which may explain why users prefer heroin over morphine for achieving rewarding effects (Oldendorf, Hyman, Braun, & Oldendorf, 1972) (**Figure 10.2**).

**FIGURE 10.2** **Blood–Brain Barrier Passage by Heroin and Morphine**

Because of its greater lipid solubility, heroin enters the brain through the blood–brain barrier more readily than morphine.




Opioids are primarily metabolized in the liver, often producing metabolites that have biological effects. Morphine, for example, produces the biologically active metabolite *morphine-6-glucuronide*, a potent analgesic that may account for many of morphine's analgesic effects (Christrup, 1997). We also find morphine as a metabolite of codeine and a secondary metabolite of heroin. For codeine, the cytochrome P450 enzyme CYP2D6 is responsible for converting approximately five percent of codeine to morphine. We find more metabolic production morphine taking place for those with high CYP2D6 activity, however, suggesting that some individuals, particularly children, are prone to overdose from codeine (Ortiz de Montellano, 2013).

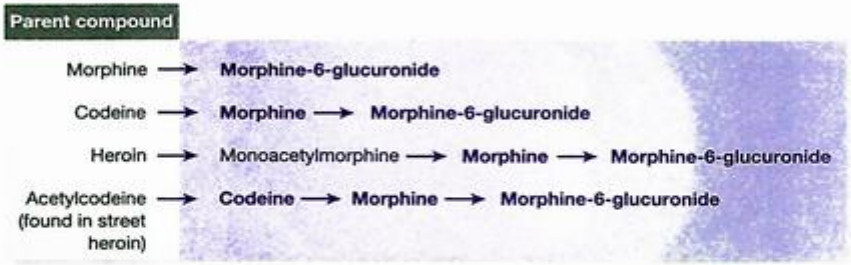
Opioid metabolites provide key indicators of opioid use and are detectable in urine samples. However, the presence of opioid metabolites may not identify the exact opioid used. For example, morphine is a metabolite of codeine and a secondary metabolite of heroin (Rook, Hillebrand, Rosing, van Ree, & Beijnen, 2005; Yeh & Woods, 1970) (**Figure 10.3**). Thus, the presence of morphine in a urine sample could suggest morphine, codeine, or heroin use, but not the exact drug used.

If a technician needs to identify the precise opioid used, then she or he must test for other metabolites. For example, heroin is metabolized to *monoacetylmorphine*, which is then converted to morphine. The presence of both monoacetylmorphine and morphine might suggest heroin use. In addition, street heroin often includes acetylcodeine, which is metabolized to codeine. The added presence of codeine in a urine analysis would further indicate heroin use.

The elimination rate of opioids varies from drug to drug. Many heroin cessation programs prescribe patients methadone, partly because of methadone's long elimination rate. Methadone levels peak in the body several hours after administration

**FIGURE 10.3 Active Metabolites of Selected Opioids**

Many opioid drugs have active metabolites, often including morphine. The active metabolites appear in bold.




and remain at biologically active levels 24 hours after administration (Vos, Ufkes, Wilgenburg, Geerlings, & Brink, 1995). Although methadone remains in the body, it functions to prevent heroin withdrawal symptoms from occurring. The semisynthetic opioid buprenorphine also exhibits a weak euphoric effect and offers long elimination rate. Given these traits, opioid cessation programs also use buprenorphine as a substitute for an addictive opioid drug (Comer, Collins, & Fischman, 2001).

## STOP & CHECK

1. Opioids are usually administered orally, intravenously, or through _____.
2. What is a common active metabolite of many opioid drugs?

1. inhalation 2. morphine and morphine-6-glucuronide

## Opioid Drugs and the Endogenous Opioid System

The endogenous opioid system includes opioid neurotransmitters and receptors. Endogenous opioids are neuropeptide neurotransmitters. The amino acids linked together to make up each neuropeptide are part of a large chain of amino acids referred to as a **propeptide.** We use the term *cleavage* to refer to the separation of a peptide segment from a longer propeptide.

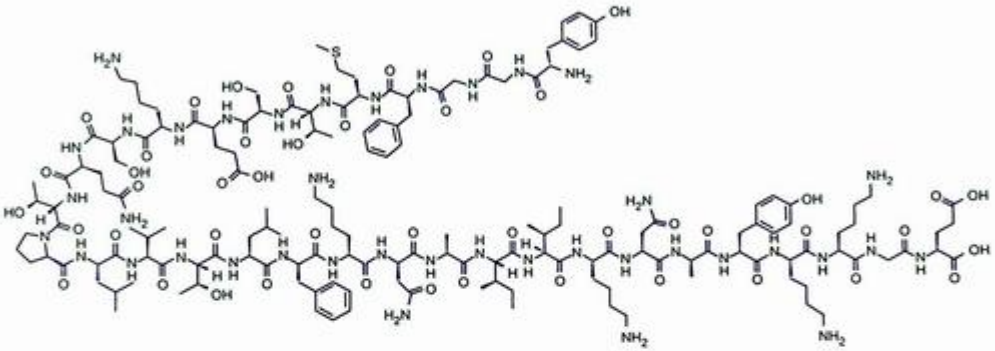
**Propeptide**
Chain of amino acids containing one or more peptides

The endogenous opioid neuropeptides consist of β-endorphin, met-enkephalin, leu-enkephalin, dynorphin A, dynorphin B, and neoendorphin. These endogenous opioid neuropeptides derive from three propeptides: proopiomelanocortin,

proenkephalin, and prodynorphin. Cleavage of proopiomelanocortin produces β-endorphin (**Figures 10.4** and **10.5**). Met-enkephalin and leu-enkephalin come from proenkephalin, and cleavage of prodynorphin produces dynorphin A, dynorphin B, and neoendorphins (Chavkin, James, & Goldstein, 1982; Comb, Seeburg, Adelman, Eiden, & Herbert, 1982; Hughes, Smith, Morgan, & Fothergill, 1975).

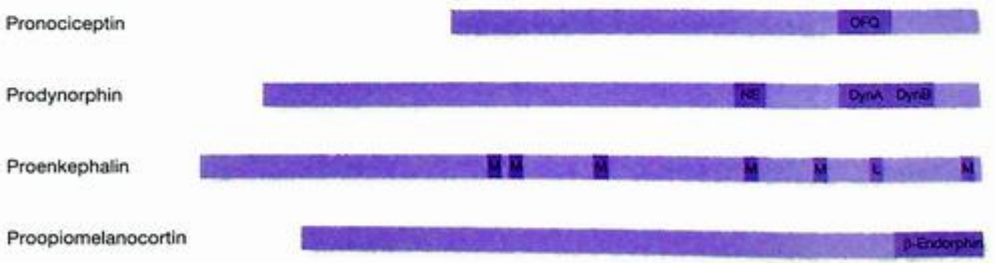
## FIGURE 10.4 Chemical Structure for β-Endorphin

The endogenous opioid β-endorphin comprises 31 amino acids. A strand of amino acids is called a *peptide*, and shorter peptides such as β-endorphin are "cleaved" from longer peptides called *propeptides*. To better illustrate the origin of opioid peptides, the schematics shown in Figure 10.5 are commonly used.



## FIGURE 10.5 Opioid Propeptides and Constituent Peptides

These schematics illustrate propeptides and constituent peptides. The dynorphin A and B peptides are represented as a segment of the propeptide prodynorphin. There are multiple leu- and met-enkaphalin peptides found on proenkephalin, and β-endorphin is a peptide found on proopiomelanocortin. OFQ = orphanin FQ, NE = neoendorphin, DynA = dynorphin A, DynB = Dynorphin B, M = met-enkephalin, and L = leu-enkephalin.



The endogenous opioids bind to three types of opioid receptors: μ (pronounced "mu"), δ ("delta"), and κ ("kappa") receptors. β-endorphin, met-enkephalin, and leu-enkephalin bind to μ and δ opioid receptors. The dynorphin and neoendorphin neurotransmitters selectively bind to κ receptors (**Table 10.3**). Most of the pharmacological effects associated with opioids are derived through activating μ and δ receptors (Mansour, Hoversten, Taylor, Watson, & Akil, 1995; Trigo, Martin-García, Berrendero, Robledo, & Maldonado, 2010). Kappa receptors, however, elicit hallucinogenic effects (Roth et al., 2002). A kappa receptor drug called *salvinorin A* is discussed in Chapter 12.

The endogenous opioid system may also include the neuropeptide *nociceptin*. Nociceptin, also known as *orphanin FQ*, is produced from prepronociceptin and binds to the opioid receptor-like-1 (ORL-1) receptor. The ORL-1 receptor is also called the *nociceptin receptor*. The structure of the ORL-1 receptor is similar to other opioid receptors, supporting the case that nociceptin is another opioid neurotransmitter.

Beyond these structural similarities, activation of the ORL-1 receptor exhibits pharmacological effects that oppose those produced from other opioid receptors. In particular, the activation of ORL-1 receptors can limit the analgesic effects produced by μ opioid receptor agonists, such as morphine. The location of ORL-1 receptors may account for these and other opposing effects. ORL-1 receptors are either located on different neurons than other opioid receptors or found on a different part of the neuron where other opioid receptors are located (Meunier, 1997).

**G-protein-coupled inwardly rectifying K+ channel (GIRK)** A $K^+$ channel that causes the influx of $K^+$ when a neuron is hyperpolarized and less $K^+$ influx when a neuron is depolarized

Opioid receptors, including the ORL-1 receptor, are G-protein-coupled metabotropic receptors. Through activation of G proteins, these receptors *reduce* metabolic activity within neurons. As a result, neurons that have opioid receptors tend to have reduced neurotransmission after administration of an opioid receptor agonist. The internal neuronal mechanisms involved in these inhibitory effects are complex and not entirely identified. One known inhibitory mechanism consists of the activation of inwardly rectifying $K^+$ channels. A **G-protein-coupled inwardly rectifying $K^+$ channel (GIRK)** causes the influx of $K^+$ when a neuron is hyperpolarized and diminished $K^+$ influx when a neuron is depolarized. Through these properties, GIRKs help maintain a neuron's resting potential. When these

**TABLE 10.3 Endogenous Opioid Neurotransmitters and Their Matching Receptors**

| Endogenous Opioid Neurotransmitter | Receptor Activated |
|---|---|
| β-endorphin | μ (mu) δ (delta) |
| Met-enkephalin and leu-enkephalin | μ δ |
| Dynorphin A & B | κ (kappa) |
| Neoendorphins | κ |
| Nociceptin | ORL-1 |

membrane channels are activated, which happens from activation of ORL-1 receptors, a neuron's membrane potential approaches a resting potential (Meunier, 1997; Trigo et al., 2010).

**Review!** A resting potential describes a negatively charged local potential that precedes an action potential (Chapter 3).

Adaptation occurs to opioids during repeated administration. One of these processes involves a reduction in sodium–potassium pump activity. By reducing this activity, a neuron membrane adapts to the inhibitory effects of opioids by depolarizing the membrane. This increases the excitability of a neuron, which serves to counteract an opioid drug's inhibitory effects. When an opioid drug is not present, this state of depolarization increases a neuron's activity, accounting for certain withdrawal effects noted later in this chapter (Trigo et al., 2010).

**Review!** The sodium–potassium pump maintains a negative resting state potential by expelling three $Na^+$ ions for every two $K^+$ ions brought into a neuron (Chapter 3).

## STOP & CHECK

1. Endogenous opioids are cleaved from four different _____.
2. Opioid receptors are G-protein-coupled receptors that produce _____ effects on neurons.

1. propeptides 2. inhibitory

## Opioid Drugs Are Classified by Receptor Actions

Most of the opioid drugs used, either recreationally or instrumentally, act on $\mu$ opioid receptors. We also find that opioid drugs can have different actions at opioid receptors, and this in turn accounts for different pharmacological effects across compounds. Given this, opioids also are classified by their receptor actions.

Drugs identified as **pure opioid receptor agonists** produce full agonist actions at $\mu$ opioid receptors. Many of these drugs also act as full agonists at other opioid receptors too. Fentanyl and morphine are examples of pure opioid receptor agonists (DeWire et al., 2013; Hughes, Kosterlitz, & Leslie, 1975). In some experiments on the pharmacodynamic actions of opioids, morphine produces weaker effects compared to synthetic drugs, such as fentanyl, causing some to label morphine as a

**Pure opioid receptor agonists** Drugs that act as full receptor agonists at $\mu$ opioid receptors

partial agonist instead (DeWire et al., 2013). Yet, compared to other classifications for receptor agonists considered here, morphine fits far better in the pure opioid receptor agonist category than as a partial opioid receptor agonist.

**Partial opioid receptor agonists**
Drugs that produce partial agonist actions at μ opioid receptors

**Partial opioid receptor agonists** produce partial agonist actions at μ opioid receptors and therefore a smaller magnitude of pharmacological effects compared to pure opioid receptor agonists. Buprenorphine is classified as a partial opioid receptor agonist and exhibits weaker pharmacological effects compared to morphine (Virk, Arttamangkul, Birdsong, & Williams, 2009). For example, Dahan and colleagues (2006) found that even though buprenorphine exhibited gains in pain-relieving effects as they raised the dose in human volunteers, a ceiling effect was reached for respiratory depressant effects. Thus, they concluded that buprenorphine serves as an analgesic opioid drug that fails to cause significant impairments in breathing.

**Review!** Partial agonists have a lower efficacy for activating receptors than full agonists do (Chapter 4).

**Pure opioid receptor antagonists**
Drugs that act as full receptor antagonists at μ opioid receptors

**Pure opioid receptor antagonists** act as full-receptor antagonists at μ opioid receptors. These drugs not only fail to produce opioid pharmacological effects but also inhibit opioid system activity by preventing endogenous opioids from binding to opioid receptors. They also counteract the effects produced by drugs acting as full or partial opioid receptor agonists. Physicians prescribe pure opioid receptor antagonists for treating opioid addiction (Fudala & Woody, 2002). The "From Actions to Effects" section describes this and other approaches for treating opioid addiction.

**Mixed opioid receptor agonist–antagonists**
Drugs that exhibit agonist actions at some opioid receptors while exhibiting antagonist actions at other opioid receptors

The final type of an opioid drug is a mixed opioid receptor agonist–antagonist. **Mixed opioid receptor agonist–antagonists** exhibit agonist actions at some opioid receptors while exhibiting antagonist actions at other opioid receptors. Together, these actions limit the magnitude of opioid pharmacological effects. For example, the mixed opioid receptor agonist–antagonist *pentazocine (Talwin)* exhibits a ceiling effect for reducing pain (Shu et al., 2011). Many opioids were once classified as mixed receptor agonist–antagonists but have since been found to act through other mechanisms such as partial agonism or other receptors such as the recently discovered ORL-1 opioid receptor.

Buprenorphine is an opioid drug found to act through many mechanisms. First, as stated earlier, buprenorphine acts as a partial agonist at μ opioid receptors. Second, buprenorphine is an antagonist for δ receptors. Third, it has as an active metabolite norbuprenorphine, which acts as a full agonist for both μ and δ receptors.

A fourth mechanism may contribute to buprenorphine's ceiling effects for pain. Buprenorphine is an agonist for the ORL-1 receptor. Activation of the ORL-1 receptor counteracts the pharmacological effects produced by the activation of other opioid receptor types. Thus, ORL-1 receptor activation opposes the effects produced through μ and δ receptor activation, accounting for buprenorphine's limiting effects for pain (Lufty & Cowan, 2004).

## Drug Profile: buprenorphine

| | |
|---|---|
| Brand name | *Subutex* |
| Mechanisms of action | 1. Partial agonist for μ receptors<br>2. Antagonist for δ receptors<br>3. Active metabolite, norbuprenorphine, acts as agonist for μ and δ receptors<br>4. Agonist for ORL-1 receptors |
| Uses | Used for treating opioid addiction and for pain |

Different mechanisms of action produced by opioid receptors produce different discriminative stimulus effects (see Box 6.1 to review the drug discrimination procedure). This was demonstrated in a study by Platt, Rowlett, Izenwasser, and Spealman (2004) using rhesus monkeys trained to discriminate the stimulus effects of heroin, a pure opioid receptor agonist (**Figure 10.6**). In these monkeys, full opioid receptor agonists produced heroin-like stimulus effects, whereas an experimental μ opioid receptor partial agonist called 3-MNTX produced weak heroin-like stimulus effects.

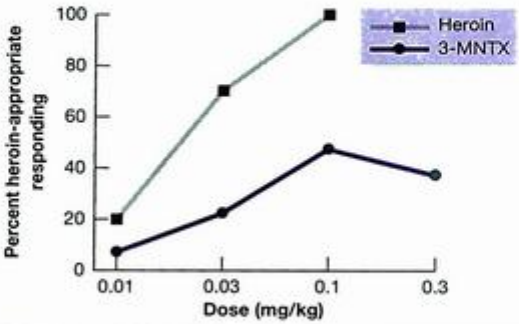
## STOP & CHECK

1. An opioid drug with a ceiling effect for pain relief is likely a(n) _____ .
2. Opioid receptors are G-protein-coupled receptors that produce _____ effects on neurons.
3. Should buprenorphine still be considered a representative drug for partial opioid receptor agonists?

1. partial opioid receptor agonist; 2. inhibitory 3. Although buprenorphine is still classified as a representative of the partial opioid receptor agonist class of drugs, it exhibits many other actions that may alternatively account for its pharmacological effects. In particular, buprenorphine's ceiling effect can be accounted for not only through partial opioid receptor agonism but also through antagonism of δ receptors and activation of ORL-1 receptors.

**FIGURE 10.6** **The Subjective Effects of a Partial Opioid Agonist Are Weaker Than a Full Opioid Agonist**

In monkeys trained to discriminate the stimulus effects of heroin, heroin produced 100 percent heroin-appropriate responding, whereas the μ opioid receptor partial agonist 3-MNTX produced fewer heroin-appropriate responses. The *y*-axis shows the percentage of heroin-appropriate responses made, and the *x*-axis shows the dose of 3-MNTX or heroin tested.




*Source:* Data from Platt et al. (2004).

## Opioids and Reward, Pain, and Stress Systems

Endogenous and exogenous opioids produce reinforcing effects by affecting dopamine and GABA neurotransmission. Opioids increase dopamine release primarily by binding to μ opioid receptors on GABA neurons in the ventral tegmental area. **Figure 10.7** shows the series of actions involved in this reward circuitry.

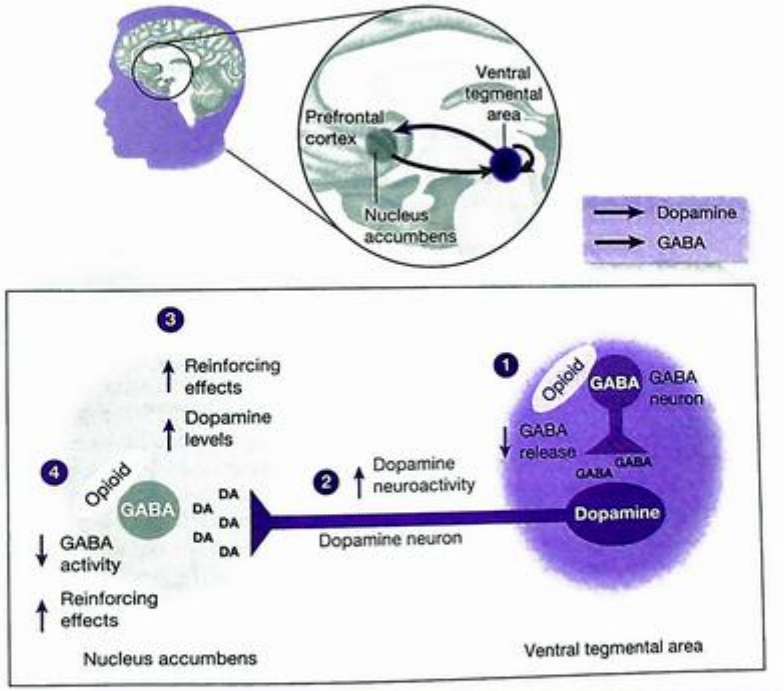
**Review!** The ventral tegmental area contains dopamine neurons, which send axons to the nucleus accumbens, other parts of the limbic system, and the cerebral cortex (Chapter 3).

First, opioids inhibit the activity of GABA neurons in the ventral tegmental area. By doing so, there is less GABA released in the ventral tegmental area to activate inhibitory GABA receptors on mesolimbic dopamine neurons. By removing this inhibition on dopamine neurons, the activity of dopamine neurons increases, leading to greater dopamine release in the nucleus accumbens (McBride, Murphy, & Ikemoto, 1999; Omelchenko & Sesack, 2010; Wise, 1989).

Second, opioids produce rewarding effects through activating μ opioid receptors in the nucleus accumbens. The majority of μ opioid receptors in the nucleus accumbens are found on GABA neurons. Drugs that act as opioid agonists activate inhibitory opioid receptors, leading to an inhibition of these GABA neurons. Many of these GABA neurons project to the ventral tegmental area, where they

**FIGURE 10.7 Opioids and Reward Circuitry**

Opioids produce reinforcing effects by acting on dopamine and GABA neurons in either the ventral tegmental area or the nucleus accumbens: (1) this occurs through an opioid's activation of opioid receptors on GABA neurons in the ventral tegmental area, causing reduced GABA release and reduced activation of GABA receptors on dopamine neurons; (2) this in turn increases the activity of dopamine neurons; (3) this causes increased dopamine release in the nucleus accumbens, an action that increases reinforcing effects; and (4) an opioid's activation of opioid receptors on nucleus accumbens GABA neurons causes a reduction in GABA neuron activity, an action associated with increased reinforcing effects.




may contribute to the inhibition of dopamine neurons as just described (Kalivas, Churchill, & Klitenick, 1993; McBride et al., 1999; Svingos, Moriwaki, Wang, Uhl, & Pickel, 1997; Wise, 1989).

Due to these interactions with reward pathways, antagonists for opioid receptors have been evaluated as treatments for substance addictions. For example, in amphetamine-addicted users, naltrexone has been shown to reduce cravings for amphetamine and decrease amphetamine use compared to placebo (Jayaram-Lindström,

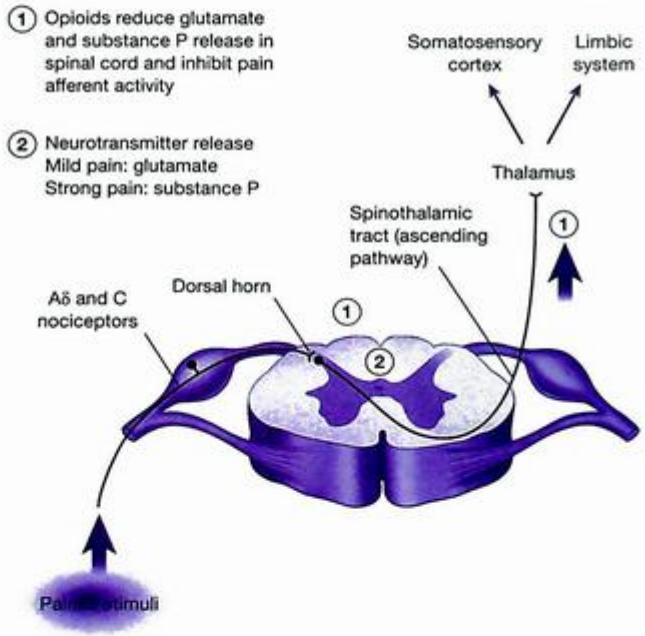
Hammarberg, Beck, & Franck, 2008). We find similar data for naltrexone for tobacco smokers. In one study, during 12 weeks of naltrexone treatment, study participants reported fewer cravings to smoke and many quit smoking completely. Upon discontinuing naltrexone treatment, smoking returned to pre-naltrexone treatment levels (King et al., 2012).

**Nociception**
Communication of pain sensations in the nervous system

Opioids also closely interact with pain signalling pathways to the brain, as shown in **Figure 10.8**. We can think of the communication of pain sensations in the nervous system, referred to as **nociception**, as a relay involving two pathways. The first pathway has two types of axons, referred to as *Aδ fibers* and *C fibers*, that communicate nociceptive information from the source of a painful stimulus to the dorsal horn of the spinal cord. Within the dorsal horn, these pathways release

## FIGURE 10.8 Opioids and Pain Signalling

Opioids inhibit nociception by inhibiting glutamate and substance P release in the dorsal horn of the spinal cord and by decreasing the activity of neurons communicating pain information to the brain.



the neurotransmitters glutamate and *substance P* at postsynaptic terminals on spinothalamic neurons. During inflammation or after suffering a trauma, enhanced pain sensitivity—called *hyperalgesia*—may occur because of a process of synaptic strengthening called *long-term potentiation* (described in detail in Chapter 12) (Ikeda et al., 2006). This process results in greater pain signalling between the Aδ and C fibers and the spinothalamic neurons.

Second, spinothalamic neurons send nociceptive information via an *ascending pathway* to the thalamus. The thalamus, in turn, distributes the information to the somatosensory cortex and two structures in the limbic system: the cingulate cortex and the amygdala. The somatosensory cortex processes the nociceptive information, while the cingulate cortex and amygdala produce emotional responses to pain and play a role in approach and avoidance behavior (Watkins, Milligan, & Maier, 2001; Willis & Westlund, 1997).

**Review!** The peripheral nervous system sends sensory information to the dorsal horn of the spinal cord, whereas motor information comes from the ventral horn of the spinal cord (Chapter 2).

Opioids weaken neurotransmission within these pain pathways. First, all four types of opioid receptors reside on C and Aδ axon terminals. The activation of these opioid receptors causes a reduction in glutamate and substance P release, thereby reducing pain signalling (Chen & Sommer, 2006; Ossipov et al., 2004). Chronic administration of opioids appears to produce long-term potentiation as a compensatory action for these inhibitory effects. Similar to long-term potentiation seen with inflammation and trauma, long-term potentiation causes enhanced pain sensitivity when opioid use ceases (Drdla, Gassner, Gingl, & Sandkuhler, 2009). Second, neurons from the periaqueductal gray release endogenous opioids in the medulla, which contains a high density of $\mu$ opioid receptors. Activating opioid receptors in the medulla inhibits the activity of spinothalamic neurons passing through the medulla, thus reducing nociceptive information flow to the thalamus (Ossipov et al., 2004).

**Review!** Periaqueductal gray surrounds the cerebral aqueduct, a conduit for cerebrospinal fluid connecting the third and fourth ventricles in the brain (Chapter 2).

Opioid receptors are found outside the nervous system as well, including the immune, cardiovascular, respiratory, and digestive systems (Stein, Schafer, & Hassan, 1995). These peripheral actions contribute to inhibition of respiration, cardiovascular function, and digestion by opioid receptor agonists. Chronic administration of an opioid agonist suppresses immune system functioning by reducing the reproduction of immune system cells (Roy & Loh, 1996).

## STOP & CHECK

1. What effect do opioids have on GABA neurons?
2. What effect do opioids have on Aδ fibers and C fibers, which relay pain signals to the spinal cord?

1. We find inhibitory opioid receptors on GABA neurons; when the opioids bind to these receptors, the activity of GABA neurons decreases (i.e., inhibitory effects). 2. Opioids bind to inhibitory opioid receptors on these neurons, which reduces pain signaling in the form of reduced glutamate and substance P release from these neurons.

# Opioid Rewarding and Analgesic Effects

## Opioid Receptor Agonists and Rewarding Effects

The positive subjective effects of an opioid receptor agonist occur during four phases (**Table 10.4**). The *rush* phase is the initial and rapid onset of euphoria that occurs within seconds of an intravenous injection of heroin or other opioid that readily crosses the blood–brain barrier. The rush is a key achievement for opioid recreational use. As the rush subsides, a second phase called the *high* sets in, which is generally characterized by feelings of euphoria. A third phase is occasionally referred to as a *nod* and is characterized by calm, disinterest, and unawareness of surroundings. During the nod phase, anxiety is lifted and users may doze in a light sleep. Although the nod is different from euphoria, many users find this relaxed state to be quite enjoyable. Finally, the fourth phase is referred to as *straight* and consists of a period of normalcy between craving an opioid and feeling the euphoric or other positive effects of an opioid (Agar, 1974).

Based on surveys in humans, users report a number of positive subjective effects from opioid receptor agonists. In one such study, Preston, Bigelow, and Liebson (1988) assessed the subjective effects of the opioid receptor agonist hydromorphone

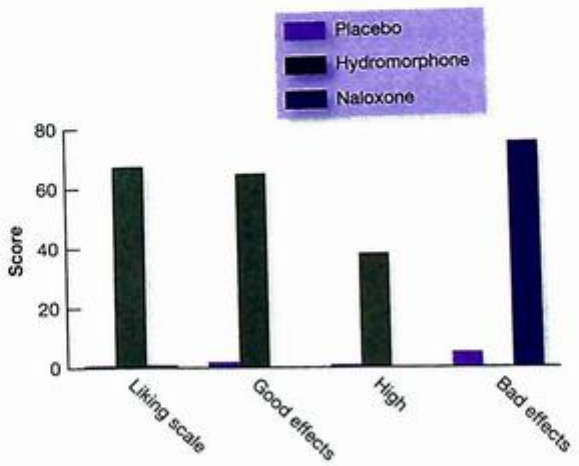
**TABLE 10.4 Subjective Effects of Opioid Agonists**

| Phase | Description |
|---|---|
| Rush | Initial and rapid onset of euphoria |
| High | Feelings of joy and ease |
| Nod | Calm, disinterest, and unawareness of surroundings |
| Straight | Period of normalcy between craving an opioid and feeling the euphoric or other positive effects of an opioid |

by using questionnaires to rate the degree of *liking, high, good effects,* and other terms associated with a positive subjective experience in study participants currently taking methadone for opioid addiction. When asked to rate these effects some minutes after hydromorphone administration, all participants rated hydromorphone as highly enjoyable, according to these scales. The participants also were surveyed after receiving an injection of the opioid receptor antagonist naloxone. After this treatment combination, the participants no longer recorded increases in liking, high, or good effects; instead, they reported bad effects, likely because of naloxone triggering opioid withdrawal effects (**Figure 10.9**). Self-administration procedures in animals also indicate that opioid receptor agonists produce potent rewarding effects. Further, the duration of these reinforcing effects alters drug-seeking behavior. A self-administration study conducted by Panlilio and Schindler (2000) demonstrated these properties (**Figure 10.10**). In this study, rats were assessed on a progressive ratio schedule for intravenous injections of an opioid. In one group of rats, the opioid was heroin; in another group of rats, the opioid was *remifentanil (Ultiva)*. Remifentanil exhibits similar actions to heroin, except that remifentanil has an elimination half-life of only 40 seconds.

**FIGURE 10.9** **Subjective Effect Ratings for an Opioid Agonist and an Antagonist**

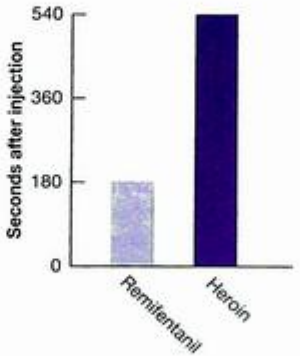
Study participants currently in treatment for opioid addiction were asked to rate the subjective effects (liking the effects [indicated by higher numbers on a liking scale], good effects, feeling a high, or bad effects) of the opioid agonist hydromorphone, the opioid antagonist naloxone, and placebo conditions. Respondents endorsed positive effects for hydromorphone and bad effects for naloxone.




Source: Data from Preston, Bigelow, and Liebson (1988).

**FIGURE 10.10** **Self-Administration in Rats for Heroin and the Short-Acting Opioid Remifentanil**

During a self-administration study, rats resumed responding more quickly after receiving an injection of the short-action opioid agonist remifentanil than rats after receiving an administration of heroin. The *y*-axis shows the number of seconds between an injection and a following response.




*Source:* Data from Panlilio and Schindler (2000).

Both heroin and remifentanil achieved similar break points in this study, but the remifentanil rats reached the break point much sooner than the heroin rats because of a much shorter post-reinforcement pause during responding for remifentanil. Because the rewarding effect of remifentanil was short lived, the rats quickly returned to lever pressing after every injection, thus shortening the post-reward pause. Heroin-treated rats had longer periods of time between receiving an injection and when they resumed lever pressing.

The subjective effects of opioids readily pair with environmental stimuli, which researchers demonstrate using a conditioned place preference procedure (see **Box 10.1**). This procedure is often used to study the reinforcing effects of opioids, such as heroin. For example, Spyraki, Fibiger, and Phillips (1983) used a conditioned place preference procedure to study the effects of heroin administration in rats. A single dose of heroin was paired with one compartment of a shuttle box, and the heroin vehicle was paired with the opposite compartment for four days each. After pairing, rats spent significantly more time in the heroin-paired environment than the vehicle-paired environment (**Figure 10.11**). A preference for the drug compartment implies an association between the compartment and heroin's reinforcing effects.

# BOX 10.1

## CONDITIONED PLACE PREFERENCE

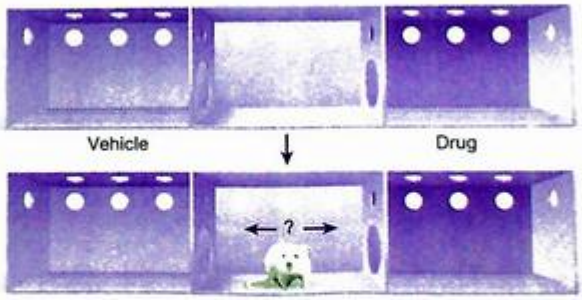
During a *conditioned place preference* procedure, an organism associates a unique environment with a drug's reinforcing effects. Researchers typically conduct this procedure with rats or mice using a shuttle box. Most shuttle boxes have two or three connected compartments with doorways between each compartment, as shown in **Box 10.1 Figure 1**. Researchers design each compartment to have a different appearance (e.g., white walls versus black walls), floor texture (e.g., horizontal bars versus a wire grid), and odor in the compartment waste pans (e.g., pine shavings versus cellulose bedding).

A conditioned place preference develops over the course of several pairings with a reinforcing drug. Generally, researchers devote three to five pairing sessions with a drug's rewarding effects and a specific shuttle box compartment. Other pairing sessions occur with the drug's vehicle and the opposite compartment. After drug- and vehicle-pairing sessions, researchers place a trained animal into the shuttle box with all compartment doors raised, allowing the animal free access to any compartment. A conditioned place preference is shown when rats spend significantly more time in the drug-paired compartment than in the vehicle-paired compartment.

To demonstrate the process of conditioned place preference, Mucha, van der Kooy, O'Shaughnessy, and Bucenieks (1982) conducted four pairing sessions with an intravenous morphine or saline injection given four minutes before the session. Each compartment contained different environmental stimuli. After conducting four daily sessions each with morphine and saline, rats were placed in the chamber without an injection and allowed to explore both compartments. Rats spent significantly more time in the morphine-associated compartment than the saline-associated compartment (**Box 10.1 Figure 2**).

**BOX 10.1 FIGURE 1** **A Shuttle Box for Conditioned Place Preference Procedures**

After pairing different parts of a shuttle box with either drug or vehicle (top row), researchers test for a conditioned place preference by placing a subject in a neutral part of the box and allowing the subject to freely explore the shuttle box chambers.



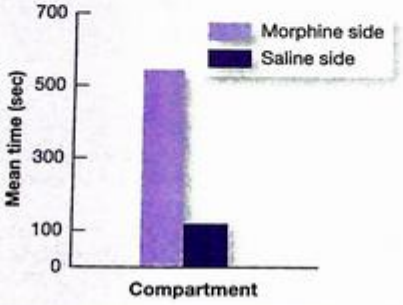

*(Continued)*

(Continued)

Next, Mucha and colleagues (1982) conducted the same procedure with the noxious substance lithium chloride. After several pairings, rats spent significantly more time in the saline-paired compartment (**Box 10.1 Figure 3**). In this case, the researchers demonstrated a *conditioned place aversion*. During a conditioned place aversion procedure, an organism associates a unique environment with a drug's aversive effects. In this case, animals avoid the drug-paired side.

## BOX 10.1 FIGURE 2 Conditioned Place Preference for Morphine

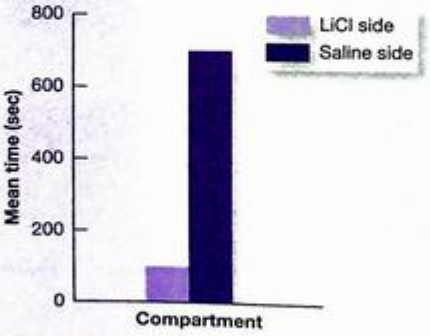
Rats spent significantly more time in a morphine-paired compartment than a saline-paired compartment, demonstrating a conditioned place preference. The *y*-axis represents time spent in a compartment, and the *x*-axis represents the dose of morphine administered. Purple bars refer to the morphine compartment.




*Source:* Mucha et al. (1982).

## BOX 10.1 FIGURE 3 Conditioned Place Aversion for Lithium Chloride

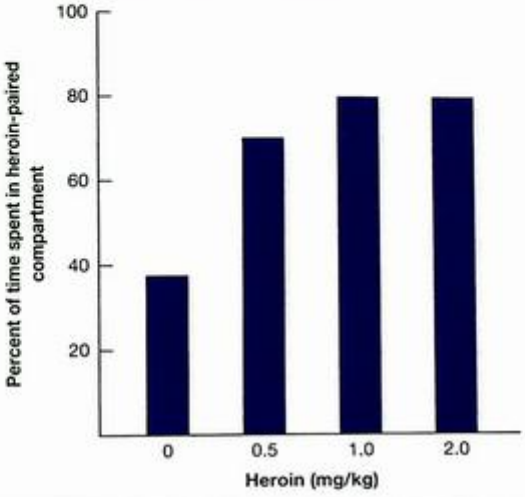
Rats spent significantly more time in a saline-paired compartment than a lithium chloride-paired compartment, demonstrating a conditioned place aversion. The *y*-axis represents time spent in a compartment. Light blue bars refer to the lithium chloride compartment.




*Source:* Adapted from Mucha et al. (1982).

**FIGURE 10.11 Conditioned Place Preference for Heroin**

After pairing sessions were completed in a conditioned place preference procedure, rats preferred the shuttle box compartment associated with heroin's pharmacological effects compared to the compartment not associated with these effects. The *y*-axis shows the percentage of time spent in the heroin-paired compartment. The *x*-axis shows the doses of heroin tested; a zero (0) dose refers to vehicle.



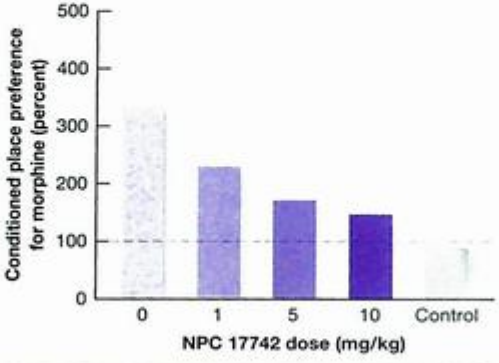

*Source:* Adapted from Springer Science+Business Media: Spyraki, C., Fibiger, H. C., & Phillips, A. G. (1983). Attenuation of heroin reward in rats by disruption of the mesolimbic dopamine system. *Psychopharmacology, 79*(2), 278–283. doi:10.1007/bf00427827, p. 6.

**Review!** A *vehicle* is the solvent in which a drug is dissolved. Functionally, a vehicle is a placebo (Chapter 1).

Researchers have also found a role for glutamate NMDA receptors in the rewarding effects of opioids using the conditioned place preference procedure. In a study conducted by Popik and Kolasiewicz (1999), a conditioned place preference for morphine was established in rats (**Figure 10.12**). In the test session, in which rats were given the choice to move freely between the morphine- and vehicle-paired compartments, these researchers treated rats with a glutamate NMDA receptor antagonist called NPC17742. NPC17742 caused rats to have a significantly lower preference for the morphine-paired compartment. This reduction in preference for the morphine-paired compartment also occurred when NPC17742 was directly injected into the ventral tegmental area or the nucleus accumbens. Because this compound functioned as an antagonist for NMDA receptors, these researchers concluded that NMDA receptor agonism may, therefore, facilitate morphine's reinforcing effects. These findings coincide with neurobiological models of addiction described in Chapter 5.

**FIGURE 10.12** **NMDA Receptor Antagonism Prevents Recall of Morphine CPP**

Blockade of glutamate NMDA receptors using the NMDA receptor antagonist NPC17742 prevents the recall of the morphine preference for one side of a shuttle box compartment. Glutamate release is an important contributor to opioid addiction.




*Source:* Adapted from Springer Science+Business Media: Popik, P., & Kolasiewicz, W. (1999). Mesolimbic NMDA receptors are implicated in the expression of conditioned morphine reward. *Naunyn-Schmiedeberg's Archives of Pharmacology, 359*(4), 288–294. doi:10.1007/pl00005354, p. 7.

**Review!** During drug addiction, glutamate levels are elevated in mesolimbic dopamine structures, including the nucleus accumbens and ventral tegmental area. Increased glutamate levels lead to increased activation of glutamate NMDA receptors (Chapter 5).

Self-administration studies also reveal a role for glutamate in the rewarding effects of an opioid. For example, LaLumiere and Kalivas (2008) assessed the effects of a reinstatement period in rats that learned to self-administer heroin. After initiating reinstatement with an administration of heroin, microdialysis procedures revealed that nucleus accumbens concentrations of glutamate increased. After finding these changes in glutamate levels, these researchers next found that inhibiting glutamate neurons that innervate the nucleus accumbens prevented heroin reinstatement. Interpreting these findings in the context of drug addiction models presented in Chapter 5, inhibition of glutamate neurotransmission may reduce a wanting state for heroin.

**Review!** Reinstatement consists of a return to drug self-administration responding that usually occurs after an administration of the drug, presentation of a stimulus associated with the drug, or the causation of stress (Chapter 5).

**Review!** Wanting occurs when stimuli associated with drug use command attention and elicit a salient motivational state toward pursuing the drug. The most salient stimulus is the drug itself (Chapter 5).

## Opioid Analgesic Effects

As noted previously, opioids have traditionally been used for treating pain. Today, they remain the most effective medications for this purpose. Morphine, the key constituent in opium, as described previously, represents the gold standard for opioid analgesics, although physicians frequently prescribe other $\mu$ opioid receptor agonists, including oxycodone and fentanyl, for severe pain management (Gomes et al., 2011). Studies find that short-term use of opioid analgesics lacks significant efficacy for *neuropathic pain*, which is derived from damage to pain-signalling neurons, or *idiopathic pain*, which consists of pain derived from an unknown organic cause (Arnér & Meyerson, 1988). On the other hand, intermediate use has been shown to reduce these types of pain (Eisenberg, McNicol, & Carr, 2006).

A side effect found to accompany the analgesic effects of opioids is an itch sensation that provokes a desire to scratch. The technical term for an itch is *pruritus*. Scratching an itch when caused by a skin irritation can lead to removing the irritant and consequently the itch. Opioids produce a neurogenic itch, an itch derived from signalling in the nervous system, and therefore, not relieved from scratching. The effect is experienced by only one percent of those taking an opioid orally or through injection, but is far more prevalent for those receiving an opioid through spinal administration, such as an epidural opioid administration for women during labor. An itch produced by opioid agonist can be relieved by administration of an opioid antagonist. In addition, opioid-induced itch can be relieved by the serotonin ($5\text{-}HT_3$) receptor antagonist ondansetron (Twycross et al., 2003). Animal studies have found opioid-induced itch to be produced through the $\mu$ opioid receptor (Ko, Song, Edwards, Lee, & Naughton, 2004).

## Opioid Drugs and Other Therapeutic Effects

Beyond analgesia, the medicinal value of opioids is derived from other effects in the body. The inhibitory effects of opioid receptors in the intestinal tract produce constipation and provide an effective and important treatment for diarrhea. This has long been a key therapeutic use of opium, and opioid drugs are still used for this purpose today. For example, morphine is used in hospitals to reduce diarrhea associated with severe flu or other diseases (De Schepper, Cremonini, Park, & Camilleri, 2004; Shook, Lemcke, Gehrig, Hruby, & Burks, 1989).

By activating inhibitory opioid receptors in the medulla, opioids also suppress the cough reflex. Therapeutically, opioids remain a highly effective cough suppressant. The natural opioid codeine is still used in prescription-strength cough syrups (Bolser, 2006). Opioids also constrict pupils, which occurs even in low light conditions. This effect, called **miosis**, is a direct effect of opioid receptor activation and occurs at analgesic doses (Ravnborg, Jensen, Jensen, & Holk, 1987).

**Miosis**
Pupil constriction that can occur after opioid administration

## Opioid Overdose and Respiratory Function

**Opioid overdose**
Overdose from opioid use in the form of severe respiratory depression, accompanied by weakness, weak pulse, bluish color to lips and skin, inability to talk, and, potentially, unconsciousness

**Opioid overdose** comes in the form of severe respiratory depression, accompanied by weakness, weak pulse, bluish color to lips and skin, inability to talk, and, potentially, unconsciousness. Much of these overdose effects derive from impaired oxygen delivery to the body because of inhibited breathing.

Some respiratory depression also occurs at therapeutically effective doses for prescribed opioids, but this is not dangerous unless an individual suffers from a respiratory disorder such as emphysema. We also find these effects magnified by other depressant drugs such as alcohol and benzodiazepines (Horlocker et al., 2009). Respiratory depression results from inhibitory effects in the medulla, the same area responsible for cough suppression (Etches, Sandler, & Daley, 1989).

The typical emergency treatment for opioid overdose begins by determining whether ventilation support will suffice in restoring proper breathing; if not, medical staff will next administer an opioid receptor antagonist, such as naloxone, in an effort to counteract the effects of the opioid (Sporer, 1999). Once administered, naloxone produces rapid effects. If given intravenously, the counteracting effects of naloxone, which consists of stabilized increased respiration, typically become noticeable within one to two minutes; otherwise, emergency room staff may give further administrations of the drug. If a suitable vein cannot be found, as might be the case with an opioid user, or if administration is given by a first responder (e.g., a paramedic in an ambulance), staff may inject naloxone intramuscularly, which only slightly delays time of onset to approximately eight minutes. An intranasal method, sold under the brand name *Narcan*, serves as another route for emergency naloxone administration (**Figure 10.13**). Intranasal administration also provides a rapid onset

**FIGURE 10.13** Narcan

Narcan is a form of naloxone for intranasal administration, which can be used for opioid overdose.

New2net86.shutterstock.com

of drug administration, requiring approximately 10 minutes for onset for improved respiration, and a nasal spray reduces risk of infections from needle sticks for first responders (Kelly et al., 2005).

## Tolerance and Dependence With Chronic Opioid Use

Tolerance occurs with all opioid pharmacological effects during repeated opioid use. During chronic administration, users develop a physiological dependence that arises from compensatory actions that counteract an opioid drug's acute effects. These compensatory effects account for the physical withdrawal symptoms from opioids. For example, because opioids produce constipation, the related withdrawal effect is diarrhea. Opioids reduce pain, so the related withdrawal effect is increased pain sensitivity (Gossop, Bradley, & Phillips, 1987; Ossipov et al., 2004). Users also develop a tolerance for the rewarding effects of opioids, resulting in the use of escalating doses to achieve desirable effects. Psychological withdrawal effects can include drug cravings and depressed mood (Gossop et al., 1987). **Table 10.5** lists these and other withdrawal effects from opioid use.

Overdose may also occur from a failure of counteracting effects to occur (i.e., a lack of tolerance expression) among regular users. To investigate why this might occur, Siegel and colleagues (1982) carried out an experiment in rats to determine what role one's environment might play in exhibiting tolerance to heroin. The researchers gave two groups of rats incrementally increasing doses of heroin during the course of a month, so that at the end of this month, rats tolerated a relatively high dose of heroin (8.0 mg/kg). However, each group of rats received these heroin injections in different environments. The first group received injections in the animal colony room in which the animals were normally housed. The other group received its injections only in a different room that contained a speaker used to generate constant white noise (like radio static).

After completing one month of daily heroin injections in these animals, the researchers conducted an overdose test by giving each rat nearly double

**TABLE 10.5 Opioid Pharmacological Effects and Withdrawal Symptoms**

| Acute Pharmacological Effect | Withdrawal Symptom |
|---|---|
| Analgesia | Pain sensitivity |
| Constipation | Diarrhea |
| Decreased blood pressure | Increased blood pressure |
| Euphoria | Dysphoria and depression |
| Hypothermia | Hyperthermia |
| Relaxation | Restlessness |
| Respiratory depression | Hyperventilation |

Source: Based on Brecher (1972).

(15.0 mg/kg) the tolerated dose. In addition, the researchers switched the injection environments for half of the animals; that is, on the overdose test, half of the animals were treated in the same injection room, whereas the other half of the animals were treated in the different injection room.

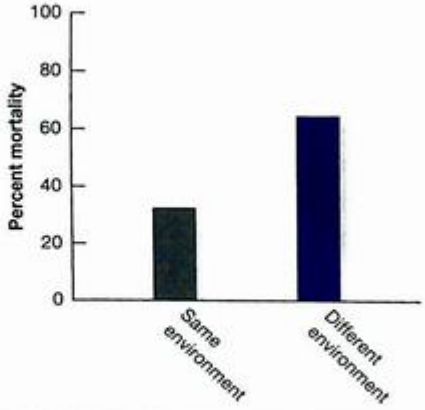
**Figure 10.14** shows the results of this experiment. The researchers found that a significantly greater number of rats died after receiving heroin in a different environment compared to rats receiving heroin in the same environment. Apparently, environmental stimuli facilitated a tolerance to heroin; when these environmental stimuli were removed, the rats demonstrated a weaker tolerance for heroin.

A link between environmental factors and conditioned tolerance may explain these findings. The researchers suggested that long-term treatment with heroin resulted in pharmacokinetic effects because of increased enzyme activity to break down heroin. By keeping the injection conditions constant, environmental stimuli occasioned the increased activity of these enzymes, providing for the creation of tolerance.

Changing the injection environment removed the stimuli associated with heroin, which possibly failed to elicit increased activation of these enzymes. With enzymes for heroin less active, less heroin was converted. Then, because much of the heroin remained in non-metabolized form in the body, the effects were similar to taking an even higher overdose of heroin. Essentially, a routine dose of heroin could in fact be an overdose of heroin without sufficient activity of these enzymes. The results suggest that heroin users who have a typical place and routine for using heroin have

**FIGURE 10.11 Tolerance Failure for Heroin in Rats**

More heroin-tolerant rats died when injected with high doses of heroin when they were in environments that were different from the ones in which they previously received injections.




Source: Based on Siegel et al. (1982).

developed a tolerance that is promoted by these environmental stimuli, a form of conditioned tolerance. Removing these stimuli may result in greater drug effects, possibly accounting for many overdose cases among opioid addicted users.

## STOP & CHECK

1. The initial and rapid euphoria produced by an opioid is referred to as a(n) _____.
2. Which neurotransmitter plays a role in addictive features of opioid use such as reinstatement and relapse?
3. In ancient times, opium was considered effective for many different ailments. Why do you suppose this was the case?
4. What type of tolerance may have been demonstrated in the study by Siegel and colleagues (1982)?
5. How might environmental stimuli changes increase the likelihood of heroin overdose?

1. rush 2. glutamate 3. Opium improved many symptoms associated with severe illness, including pain relief, diarrhea, and cough. 4. The study authors suggested that pharmacokinetic tolerance may have been weakened when the rats were injected in a different environment. 5. If tolerance failed to sufficiently occur after heroin injection as a result of changes in environment, then the body exhibits a greater sensitivity to heroin's effects. If these differences resulted from pharmacokinetic tolerance, then greater heroin amounts were more available than usual to act within the body.

## From Actions to Effects: Pharmacological Approaches for Treating Opioid Addiction

Pharmacological treatments for opioid addiction include detoxification and the management of comorbid disorders. **Detoxification** (also referred as **detoxication** or *detox*) is the first step of an opioid cessation program. Detoxification typically involves using an opioid agonist or antagonist to reduce withdrawal symptoms. Detoxification procedures vary in time course, ranging from long-term detoxification to ultra-rapid detoxification (**Table 10.6**).

**Detoxification (or detoxication)** Process that uses an opioid agonist or antagonist to reduce withdrawal symptoms

**Long-term opioid detoxification** Detoxification process that lasts approximately 180 days and occurs by prescribing an opioid receptor agonist or a partial opioid receptor agonist to replace the illicit opioid drug

**Long-term opioid detoxification** lasts approximately 180 days and occurs by prescribing an opioid receptor agonist (such as methadone or LAAM) or a partial opioid receptor agonist (such as buprenorphine) to replace the illicit opioid drug. These therapeutic opioid drugs prevent serious withdrawal symptoms, have long-lasting effects, and engender weak or no euphoria and other positive subjective effects (Gossop et al., 1987). Long-term detoxification occurs outside of hospital settings.

In the United States, the Drug Addiction Treatment Act allows doctors to prescribe schedule III, IV, and V narcotic drugs to treat opioid addiction. Thus, doctors can prescribe buprenorphine, a schedule III drug, from their offices, meaning that pharmacies can dispense this medication to a patient. This makes buprenorphine

**TABLE 10.6 Detoxification Programs**

| Detoxification Type | Opioid Receptor Treatment | Approximate Length | Facility | Withdrawal Symptoms |
|---|---|---|---|---|
| Long-term | Agonist or partial agonist | 180 days | Outpatient clinic; methadone clinic | Mild |
| Short-term | Agonist or partial agonist | 30 days | Inpatient | Moderate; may require treatment |
| Rapid | Antagonist | 10 days | Inpatient | Severe; requires treatment |
| Ultra-rapid | Antagonist | Two days | Inpatient hospital setting | Severe; requires anesthesia |

**Methadone clinics** Specialized clinics that prescribe and dispense methadone to patients in treatment for opioid addiction

**Short-term opioid detoxification** Detoxification process that lasts as long as 30 days and usually uses opioid receptor agonists

**Rapid detoxification** Detoxification process lasting as long as 10 days and using opioid antagonist administration in a treatment facility

**Ultra-rapid opioid detoxification** Detoxification process lasting as long as two days and using opioid antagonist administration in a hospital setting

more available to patients than methadone, a schedule II drug. Instead, prescribing and dispensing of methadone occurs in specialized clinics, generally referred to as **methadone clinics**. Methadone clinics must abide by regulations set by the FDA and the DEA for handling and dispensing methadone. These regulations include drug-testing clients for illicit substance use and requiring that clients have frequent contact with medical staff, counselors, and social workers.

**Short-term detoxification** programs last as long as 30 days and usually use opioid receptor agonists such as methadone and LAAM. Short-term detoxification is more aggressive than long-term detoxification and includes moderate withdrawal symptoms. These programs may be entirely conducted in an inpatient treatment facility.

**Rapid detoxification** lasts as long as 10 days, and ultra-rapid detoxification lasts as many as two days. Rapid detoxification is conducted in hospital or inpatient treatment facilities, and ultra-rapid detoxification is conducted in hospital settings. Both programs utilize an opioid receptor antagonist such as *naltrexone* or *naloxone*. Naltrexone and naloxone provide long-lasting occupancy of $\mu$ opioid receptors, preventing activation of these receptors by opioid receptor agonists such as heroin. These antagonist actions increase the severity of withdrawal symptoms but also shorten the total duration of withdrawal symptoms (Loimer, Schmid, Presslich, & Lenz, 1989).

**Ultra-rapid detoxification** uses high doses of an opioid receptor antagonist that further worsens and shortens withdrawal symptoms. Patients must be anesthetized during the most severe withdrawal effects, which occur during the first several

hours of treatment. After this, the withdrawal symptoms taper off over the course of one to two days.

By blocking opioid receptors, the body quickly adapts to the lack of opioid receptor activation. Thus, even though withdrawal symptoms are severe during rapid or ultra-rapid detoxification, they do not last as long as normal withdrawal symptoms. Moreover, many withdrawal symptoms such as diarrhea and pain sensitization are treated by medications such as *Imodium*, an antidiarrheal medication that has a small amount of the opioid agonist loperamide, or acetaminophen, an analgesic (Dupont et al., 1990). Drugs that act as $\alpha_2$ adrenoceptor agonists, such as *clonidine*, can be used to reduce hypertension, restlessness, insomnia, hostility, and other peripheral withdrawal symptoms. *Benzodiazepine* drugs can also reduce anxiety, hostility, and restlessness during opioid detoxification.

Individuals addicted to opioids may have other psychological disorders to treat, including depression or another addiction. In particular, the majority of individuals addicted to opioids have an antisocial personality disorder, and many also have borderline personality disorder (Darke, Williamson, Ross, Teesson, & Lynskey, 2004). Other common comorbid conditions include HIV infection, hepatitis B, and other medical conditions related to shared needle use or unprotected sex (Shapatava, Nelson, Tsertsvadze, & Del Rio, 2006). The risk of these medical conditions is a major rationale for "harm reduction" programs, which provide safe alternatives to risky health choices associated with illicit opioid use, including clean needle access, medical testing, and medical treatment.

As described in previous chapters, opioid and other drug addiction treatment programs offer limited success. During detoxification, many patients either discontinue treatment or return to drug use after treatment ends. As presented in Chapter 5, follow-ups five years later of patients who underwent methadone treatment revealed that most patients had resumed regular use of an opioid drug (Hubbard, Craddock, & Anderson, 2003). Other follow-up studies revealed that those who remain drug free tend to be married, better employed, better educated, and psychologically healthy (Simpson & Marsh, 1986). Although a pharmacological treatment may weaken withdrawal symptoms, medications alone may be insufficient for providing improvements in these areas of social adjustment.

## STOP & CHECK

1. During long- or short-term opioid detoxification programs, medications are provided in order to reduce the severity of _____ symptoms.
2. What type of drug is used during rapid opioid detoxification?

1. withdrawal 2. opioid antagonist

## CHAPTER SUMMARY

Opioid drugs are powerful pain-relieving and reinforcing substances used for medical and recreational purposes. Opioids are found naturally in poppy plants and can be synthesized in laboratories. Opioid drugs can be inhaled, ingested orally, or injected intravenously. Endogenous opioid neurotransmitters are peptides that bind to $\mu$, $\delta$, $\kappa$, and nociceptin receptors.

The reinforcing effects of opioids derive from elevating dopamine levels and reducing GABA neuron activity in the nucleus accumbens. Opioids inhibit pain sensation by reducing glutamate and substance P neurotransmitter release in the spinal cord and by inhibiting pain afferents to the brain. Tolerance develops quickly to opioid pharmacological effects, preventing long-term therapeutic use and requiring greater doses for recreational use.

Opioid addiction is maintained by avoiding withdrawal symptoms and achieving reinforcing effects. Detoxification programs address these components of addiction by reducing withdrawal symptoms. Long-term detoxification programs utilize a safer replacement for the illicit opioid drug, whereas rapid detoxification programs shorten withdrawal symptoms by using an opioid receptor antagonist. Treatment programs also address comorbid medical conditions.

## KEY TERMS

Opioids 317
Narcotic 317
Naturally occurring opioids 320
Semisynthetic opioids 321
Synthetic opioids (or fully synthetic opioids) 322
Laudanum 323
Propeptide 326
G-protein-coupled inwardly rectifying $K^+$ channel (GIRK) 328
Pure opioid receptor agonists 329
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CHAPTER 11

# Cannabinoids

## Chapter Outline

- Historical Use of Cannabis
- Methods of Cannabis Preparation and Use
- Cannabinoid Compounds and the Endocannabinoid System
- Physiological Effects of Cannabinoids
- Behavioral and Cognitive Effects of Cannabinoids
- Subjective Effects of Cannabinoids
- Cannabis Use Disorder
- Health Risks of Cannabis
- From Actions to Effects: Medical Use of Cannabinoids

## Learning Objectives

- Describe the types and origins of cannabinoids
- Examine the physiological actions of the endogenous cannabinoid system
- Interpret the pharmacokinetic actions of cannabis in the context of their manner and reasons for use
- Associate the pharmacological effects of cannabinoids with their pharmacological actions
- Evaluate the addiction and health risks of cannabis use
- Examine the medical uses of cannabis

**Cannabinoids**
Substances that act on cannabinoid receptors

**Cannabis**
Three varieties of plants that contain naturally occurring psychoactive cannabinoids

**Phytocannabinoids**
Cannabinoids derived from cannabis plants

**$\Delta^9$-tetrahydrocannabinol ($\Delta^9$-THC)**
Key psychoactive substance in cannabis

**Cannabinoids** consist of drugs that act on cannabinoid receptors in the nervous system and elsewhere in the body. The term *cannabinoid* comes from cannabis plants, which contain naturally occurring types of cannabinoid compounds. **Cannabis** plants come in three varieties: (1) *Cannabis sativa*, the most commonly used; (2) *Cannabis indica*; and (3) *Cannabis ruderalis*. These plants are also referred to as *hemp*, although the name refers technically to fibers of a plant and thus can describe many different types of plants.

The flowers and leaves of cannabis plants contain *trichomes*, small hair-like structures with glands that release a resin containing cannabinoid compounds. In this case, we can use the term **phytocannabinoid**, which refers to a cannabinoid compound found in plants. Phytocannabinoids include cannabis's key psychoactive ingredient, **$\Delta^9$-tetrahydrocannabinol ($\Delta^9$-THC)**, as well as other compounds such as $\Delta^8$-tetrahydrocannabinol ($\Delta^8$-THC), *cannabidiol*, cannabinol, N-alklamide, and B-caryophyllene (Gertsch, Pertwee, & Di Marzo, 2010). Among these compounds, $\Delta^9$-THC and cannabidiol have received the most attention for the pharmacological effects of cannabis.

The composition of the compounds in cannabis varies depending on the variety of cannabis, the region in which it is grown, the plant's level of maturation, and the part of the plant sampled. *Cannabis sativa* plants contain the greatest concentrations of $\Delta^9$-THC relative to other varieties, and *Cannabis indica* tends to have a relatively greater concentration of cannabidiol compared to $\Delta^9$-THC, although $\Delta^9$-THC concentrations can vary considerably (Hillig & Mahlberg, 2004). Varieties of cannabis that have no greater than 0.3 percent $\Delta^9$-THC are referred to as hemp. Trichomes appear mostly on the leaves and flowers of cannabis plants, yielding relatively higher concentrations of $\Delta^9$-THC than other phytocannabinoids.

**Marijuana (or marihuana)**
Consists of dried cannabis flowers, leaves, and stems compressed and rolled for smoking

**Marijuana** (or **marihuana**) consists of dried cannabis flowers, leaves, and stems compressed and rolled into cigarettes for smoking. Slang terms for marijuana include *weed*, *pot*, *reefer*, and *grass*. The most commonly known term for cannabis, *pot*, may derive from a Mexican slang term for marijuana, *potiguaya* (Booth, 2005). *Terpenes*, odorous organic compounds, account for marijuana's odor, which might be described as musky or skunk-like.

The $\Delta^9$-THC content in marijuana cigarettes has increased from one to as high as three percent during the 1960s and 1970s for traditional cigarettes (referred to as *reefer*) to six to 20 percent for modern cigarettes (referred to as *joints*) (Ashton, 2001; Cascini, Aiello, & Di Tanna, 2012) (see **Table 11.1** for $\Delta^9$-THC content in common cannabis products). Marijuana containing greater than 20 percent $\Delta^9$-THC has also been reported (Ahmed et al., 2008). The greater $\Delta^9$-THC content in modern marijuana cigarettes comes as a result of different cultivation methods and using types and subspecies more potent in $\Delta^9$-THC content, including *sinsemilla* (a non-pollinated female cannabis plant) and *skunk weed* (selectively bred strains of cannabis), along with using hydroponics to facilitate plant growth (Ashton, 2001). Generally, as the concentration of $\Delta^9$-THC increases, so does the ratio of $\Delta^9$-THC to cannabidiol. In the 1990s, marijuana typically had a 14-fold greater concentration of $\Delta^9$-THC to cannabidiol, but in the 2010s, this average ratio has increased to 80-fold (ElSohly et al., 2016).

E-cigarette technologies provide a modern means for using cannabis (see Chapter 7 for an overview of e-cigarette components). Unlike nicotine e-cigarettes,

**TABLE 11.1 THC Content in Cannabis Products**

| Product | THC Content |
|---|---|
| Marijuana reefer (1960s–1970s) | 1–3 percent |
| Marijuana joint | 6–20 percent |
| Hashish | 10–20 percent |
| Hashish oil | 15–30 percent |

*Source:* Adapted from Ashton (2001).

the liquid cartridge in this case includes $\Delta^9$-THC along with other components found in cannabis, such as cannabidiol. We also find these devices used for cannabidiol, often with terpenes added for aroma and flavoring. Cannabis e-cigarettes may provide a less toxic means of using cannabis because of reduced exposure to other chemicals released from burning cannabis plant material (Giroud, de Cesare, Berthet, Varlet, Concha-Lozano, & Favrat, 2015).

Another form of cannabis use is referred to as *dabbing*. **Dabbing** consists of inhaling vapors emitted from a flame-heated hashish oil and butane mixture (the "dab") that was dabbed onto the end of a glass or titanium rod. The user normally heats the dab using a blow torch. The vapors released from the dab, after heating, include concentrated $\Delta^9$-THC and other products from the mixture or heated metal (Loflin & Earleywine, 2014). As a result, $\Delta^9$-THC in vapor reaches concentrations above those smoked from cannabis, in some cases reaching up to 80 percent (Stogner & Miller, 2015). These concentrates also expose users to solvents used to extract $\Delta^9$-THC from trichomes (Sagar, Lambros, Dahlgren, Smith, & Gruber, 2018).

**Dabbing**
Inhaling vapors emitted from a flame-heated hashish oil and butane mixture (the "dab") that was dabbed onto the end of a glass or titanium rod

**Hashish** consists of a condensed, hardened preparation of cannabis that primarily contains the dried trichome resins and other parts of the plant. Given this, hashish provides a higher concentration of $\Delta^9$-THC, ranging from 10 to 20 percent. Even higher concentrations occur in oil extracted from hashish, typically referred to as *hash oil*, which can range from 15 to 30 percent and occasionally as high as 65 percent (Adams & Martin, 1996; Ashton, 2001).

**Hashish**
Condensed preparation of cannabis that primarily contains the trichome resins from the plant

In addition to the forms of cannabis just described, we also find *synthetic cannabinoids* used. **Synthetic cannabinoids** (or **synthetic marijuana**) consist of drugs that act on cannabinoid receptors, but do not consist of components from cannabis plants. Synthetic cannabinoids may be referred to by the street names *K2* and *Spice*, which may contain synthesized cannabinoid drugs, such as the compounds WIN52212-2, JWH-018, and JWH-073 (Logan, Reinhold, Xu, & Diamond, 2012; Seely et al., 2013). Synthetic cannabinoids might be used by adding them to herbs that are smoked. This form may also involve adding THC to non-cannabis herbs as well. For example, users may spray a synthetic cannabinoid compound on herbs, referred to as *herbal incense*, to smoke it like marijuana. A user may apply the substance on tobacco to smoke as well (Hu, Primack, Barnett, & Cook, 2011). Users may also inhale vapors from a synthetic cannabinoid via an e-cigarette, as described for cannabis and referred to in this case as a

**Synthetic cannabinoids (or synthetic marijuana)**
Drugs that act on cannabinoid receptors, but do not consist of components from cannabis plants

**Liquid incense (or cannabinoid-enhanced electronic liquid)** Vapors emitting from a synthetic cannabinoid liquid using an e-cigarette

**liquid incense** or **cannabinoid-enhanced electronic liquid** (Giroud et al., 2015). Another term associated with marijuana is *herbal marijuana alternative*. However, this term normally applies to using a different plant lacking in cannabinoid compounds but that might produce psychoactive effects somewhat resembling those of marijuana. For example, the plant damiana (*Turnera diffusa*) purportedly exhibits stimulant and aphrodisiac effects and is used as an herbal marijuana alternative (Kumar, Madaan, & Sharma, 2008; Szewczyk & Zidorn, 2014).

## Drug Profile: WIN52212-2

| | |
|---|---|
| Street name | *K2, Spice* (names applied to others as well) |
| Properties | WIN52212-2 is a synthetic cannabinoid receptor agonist |
| Uses | Developed by researchers to study endocannabinoid system, but now also used as a substance of abuse |

Much like bath salts (see Chapter 6), dealers market synthetic cannabinoids for seemingly benign purposes, such as potpourri or incense. Synthetic cannabinoids emerged from scientific research that endeavored to develop highly selective drugs to serve as tools for learning about the brain's endocannabinoid system (discussed later in this chapter). Because these are experimental compounds, there remains a paucity of findings about their pharmacological effects, although many reports suggest that synthetic cannabinoids exhibit different properties, such as psychostimulant or hallucinogenic effects, than traditional cannabis preparations (Rosenbaum, Carreiro, & Babu, 2012).

In the United States, as previously noted, the Drug Enforcement Administration (DEA) has classified cannabis products and synthetic cannabinoids as schedule I controlled substances. The DEA also classifies $\Delta^9$-THC as a schedule I substance, although it classifies the prescription $\Delta^9$-THC, known as *dronabinol (Marinol)*, as a schedule III controlled substance. The DEA permanently added synthetic cannabinoids as schedule I controlled substances in 2012 (**Table 11.2**).

## Drug Profile: dronabinol

| | |
|---|---|
| Brand name | *Marinol* |
| Properties | Agonist for cannabinoid CB1 receptors |
| Uses | Approved for treating nausea and vomiting during chemotherapy |

**TABLE 11.2 Controlled Substances Schedule for Selected Cannabinoid Compounds**

| Drug | Controlled Substance Schedule |
|---|---|
| Cannabis | I |
| Dronabinol (*Marinol*; synthetic $\Delta^9$-THC) | III |
| Tetrahydrocannabinol (any form of THC, including $\Delta^9$-THC and $\Delta^8$-THC) | I |
| Synthetic cannabinoids (e.g., WIN52212-2) | I |

*Source:* Adapted from the Controlled Substances Schedule found at the DEA site, http: //www.deadiversion.usdoj.gov/schedules/index.html.

Marijuana is one of the most commonly used plant-derived psychoactive substances. Approximately 3.9 percent of the world's population uses cannabis (United Nations Office of Drugs and Crime, 2018). In 2018, an estimated 124 million Americans age 12 and older reported using marijuana at least once in their lifetime, and 32 million Americans had used marijuana within the month the survey was taken (Substance Abuse and Mental Health Services Administration, 2018). Based on surveys currently available, medical marijuana laws do not appear to have caused increased marijuana use among adolescents (Lynne-Landsman, Livingston, & Wagenaar, 2013).

Laws governing the legal possession of cannabis for either recreational or medicinal uses vary widely across the globe and in the United States. Currently, cannabis possession, no matter the intended use, is illegal according to the U.S. federal government. Many individual states, however, have legalized possession of cannabis. This, in effect, places state laws in conflict with federal law, which potentially affects the willingness of businesses to enter the cannabis industry due to federal legal enforcement. The present U.S. attorney general, William Barr (Trump administration), pledged not to seek federal action against cannabis companies that comply with their state's laws, which had coincided with the perspective of the previous administration (Obama administration). Yet, the first attorney general of the Trump administration, Jeff Sessions, had declined to publicly commit to this policy, instead leaving the decision to enforce up to state federal prosecutors (subsequently reversed by William Barr). Thus, the decision to enforce or not enforce federal law regarding cannabis possession and sales depends on the current perspectives of the U.S. Attorney General's office.

Within the United States, most states (currently 33, in addition to the District of Columbia and several territories) have legalized the use of cannabis for medical purposes. Fourteen states have also legalized cannabis for recreational purposes (National Conference of State Legislatures, 2019). Overall, the laws pertain to cannabis plants and do not legalize the possession of synthetic cannabinoids.

Prevalence data for synthetic cannabinoid use is more difficult to obtain. In a survey of college students in 2010, Hu and colleagues (2011) estimated that eight percent have tried a synthetic cannabinoid. Based on surveys conducted in 2014, an estimated five percent of 12th graders have used a synthetic cannabinoid in the past year (National Institute on Drug Abuse, 2015). Some evidence suggests an increased

use of these substances. For example, over a three-day period, 41 individuals "experienced serious medical reactions" to synthetic cannabinoid products described as "Bubblegum Flavor" or "Smacked!" in Manchester, New Hampshire, causing the state governor to declare a state of emergency (Hassan, 2014). In addition, during a two-week period in 2015, New York state hospitals reported 160 patients brought in for poisoning from products identified as *Spice* or *K2* (New York State, 2015).

## STOP & CHECK

1. A preparation of *cannabis sativa* consisting mostly of dried leaves and stems is called _____.
2. The primary psychoactive ingredient in cannabis is _____.
3. _____ is a condensed form of cannabis consisting mainly of trichome resins.
4. Cannabinoid compounds invented in laboratories for the purpose of scientific research are referred to as _____.

1. marijuana 2. $\Delta^9$-THC 3. Hashish 4. synthetic cannabinoids (or synthetic marijuana)

## Historical Use of Cannabis

Like other psychoactive plants, cannabis has an ancient history. Some of the earliest records find cannabis used for medical purposes in ancient China. In 2737 B.C., Emperor Shen-Nung is said to have recommended cannabis resin for "gout, rheumatism, malaria, beriberi [*sic*] [a nervous system disorder caused by thiamine deficiency], constipation, and absent mindedness." Later in China, physician Hua-T'o wrote of a mixture of cannabis resins and wine to use as a surgical anesthetic (Emboden, 1972).

In Arabia, cannabis was commonly smoked for its mood-enhancing effects. Hashish also began to be used in this region in approximately A.D. 1100. Hashish played a critical role in a religious cult formed by Hashishin ibn al-Sabbah, who commonly went by the name al-Hasan ibn al-Sabbah (ca. A.D. 1124). During his purported travels, Marco Polo remarked in his journal about the practices al-Hasan used for recruiting men into his sect:

> Now no man was allowed to enter the Garden save those whom he intended to be his ASHISHIN. There was a fortress at the entrance to the Garden, strong enough to resist all the world, and there was no other way to get in. He kept at his Court a number of the youths of the country, from twelve to twenty years of age, such as had a taste for soldiering, and to these he used

> to tell tales about Paradise, just as Mahommet had been wont to do, and they believed in him just as the Saracens believe in Mahommet. Then he would introduce them into his Garden, some four, or six, or ten at a time, having first made them drink a certain potion which cast them into a deep sleep, and then causing them to be lifted and carried in. So when they awoke they found themselves in the Garden.
>
> When therefore they awoke, and found themselves in a place so charming, they deemed that it was Paradise in very truth. And the ladies and damsels dallied with them to their heart's content, so that they had what young men would have; and with their own good will they never would have quitted the place. (Polo, 1871, pp. 132–134)

Marco Polo expanded on his description of al-Hasan's followers and deadly tactics, writing, "When the Old Man would have any prince slain, he would say to such a youth: 'Go thou and slay So and So; and when thou returnest my Angels shall bear thee into Paradise. And shouldst thou die, natheless even so will I send my Angels to carry thee back into Paradise'" (Polo, 1871, p. 135).

The use of cannabis in modern medicine largely began from the efforts of William O'Shaughnessy, a British physician working as a professor in Calcutta, India, in 1839. During his time in India, O'Shaughnessy experimented with the medical potential of cannabis, discovering that its sedative and anticonvulsant properties improved some of the symptoms of rabies, tetanus, and cholera (Kalant, 2001). This led Western physicians to consider cannabis as a legitimate medicine.

*The Pharmacopoeia of the United States of America* lists cannabis as a medicine in volumes published from 1851 to 1942. The United States criminalized nonmedical use of cannabis in 1937 (Aggarwal et al., 2009). Even though marijuana remained legal for medical use, the Marihuana Tax Act of 1937 required patients to pay $1 per ounce of marijuana, which largely limited its medicinal use. Possibly because of this tax and declining use, later editions of the pharmacopoeia excluded cannabis from its compilation of medicines (Aggarwal et al., 2009; Kalant, 2001).

Cannabis abuse increased in the late 1950s, and by the 1960s millions of Americans had smoked cannabis. In 1969, the U.S. government under President Richard Nixon began search-and-seizure operations at the U.S.–Mexico border primarily aimed at cannabis smugglers (Brecher, 1972). The first controlled substances schedule in the United States in 1970 included cannabis under schedule I. Since then, the DEA has approved lower scheduling for cannabinoid-based medicines such as dronabinol. The lower scheduling of these medications, together with the recent emergence of medical marijuana approval in many U.S. states, has led to petitions to the DEA to lower the scheduling level of cannabis. The response to one petition came in 2011 when DEA Administrator Michele M. Leonhart rejected the request because of marijuana's "high potential for abuse," "no currently accepted medical use in treatment in the United States," and lack of "accepted safety for use under medical supervision" (Leonhart, 2011).

## STOP & CHECK

1. To which country do we trace the earliest medical uses of cannabis?

1. China

## Methods of Cannabis Preparation and Use

For both recreational and instrumental purposes, users most often administer cannabis by inhalation. To smoke cannabis, users roll a cannabis preparation in cigarette paper and then light and smoke it like a cigarette. As noted earlier, we refer to modern cannabis cigarettes as *joints* (although certainly other terms are used as well). Users may also inhale vapors from hash oil by dabbing, as described earlier (Loflin & Earleywine, 2014). Inhalation is also the preferred method for using synthetic cannabinoids, which tend to be added to herbs or tobacco for smoking (Ashton, 2001; Hu, Primack, Barnett, & Cook, 2011). Further, applying synthetic cannabinoids to e-liquid solutions allows for inhaling vapors using e-cigarettes.

Users also smoke cannabis using a water pipe device called a *hookah* or through a less elaborate pipe referred to as a *bong*. As first described in Chapter 7, water pipes entail inhaling smoke from a plant substance through water. Users deeply inhale smoke from cannabis, allowing for absorption of cannabinoids through lung tissue (Ashton, 2001).

**Contact high**
Positive subjective effects from second-hand exposure to cannabis smoke

We also find that secondhand smoke exposure to cannabis smoke causes a **contact high**, pharmacological effects from secondhand cannabis smoke. To determine the legitimacy of contact highs, Cone and Johnson (1986) evaluated subjective effects and blood plasma levels of $\Delta^9$-THC in volunteers who inhaled secondhand cannabis smoke for an hour a session. The researchers found positive subjective effect scores in the secondhand smokers as well as plasma $\Delta^9$-THC levels close to those found from actually smoking cannabis.

For oral administration, users may eat the *hashish* form of cannabis or prepare cannabis by baking it into some type of dessert, such as brownies or cookies. Hash oil also may be applied to foods for consumption or may be applied to herbs or tobacco for smoking. Another manner of consuming cannabis orally consists of heating it with water to make a tea (Hazekamp, Bastola, Rashidi, Bender, & Verpoorte, 2007). Pharmaceutical companies sell prescription dronabinol in a capsule for oral administration.

Fifty percent of $\Delta^9$-THC releases into smoke from lit cannabis. From e-cigarette liquid preparations, up to 80 percent of $\Delta^9$-THC might be inhaled from vaporized e-liquids (Giroud et al., 2015). Most of the $\Delta^9$-THC reaching the lungs absorbs into the bloodstream. Via inhalation, effects from cannabis first occur within seconds and significant effects are observed within minutes. Via oral administration, effects first

occur between 30 minutes and two hours, but slower absorption leads to a prolonged duration of effects compared to smoking cannabis (Ashton, 2001).

Approximately 25 to 30 percent of $\Delta^9$-THC reaches the bloodstream after oral administration, mainly due to first-pass metabolism in the liver (**Figure 11.1**). As are most compounds, we find $\Delta^9$-THC metabolized in the liver by P450 enzymes, and these metabolites themselves produce effects within the body. The primary metabolite of $\Delta^9$-THC is 11-hydroxy-$\Delta^9$-THC, which produces psychoactive effects similar to those of $\Delta^9$-THC (Takeda et al., 2010). $\Delta^9$-THC exhibits high lipid solubility, leading to rapid distribution into tissues in the body, including the brain, as well as an accumulation in fat. $\Delta^9$-THC in fat releases slowly over time, leading to long-term pharmacological actions (**Figure 11.2**) (Adams & Martin, 1996; Ashton, 2001).

Because of the accumulation of $\Delta^9$-THC in fats, there is a long elimination rate of $\Delta^9$-THC during sustained use. After four to five days, $\Delta^9$-THC reaches a peak concentration in fat, which then releases $\Delta^9$-THC slowly with a half-life of seven days. This half-life makes $\Delta^9$-THC detectable for as long as 30 days after ceasing repeated use (Ashton, 2001).

## STOP & CHECK

1. What are the two common administration routes for cannabis?
2. Assuming the same content of $\Delta^9$-THC, why might someone experience greater potency from inhalation than from oral administration?

1. Inhalation through smoking and oral through eating or drinking. 2. The oral administration route subjects $\Delta^9$-THC to first-pass metabolism, which limits the amount of $\Delta^9$-THC that reaches the brain.

**FIGURE 11.1** **First-Pass Metabolism of $\Delta^9$-THC**

First-pass metabolism occurring after oral consumption of a $\Delta^9$-THC product leads to significant reduction in $\Delta^9$-THC that reaches the brain.

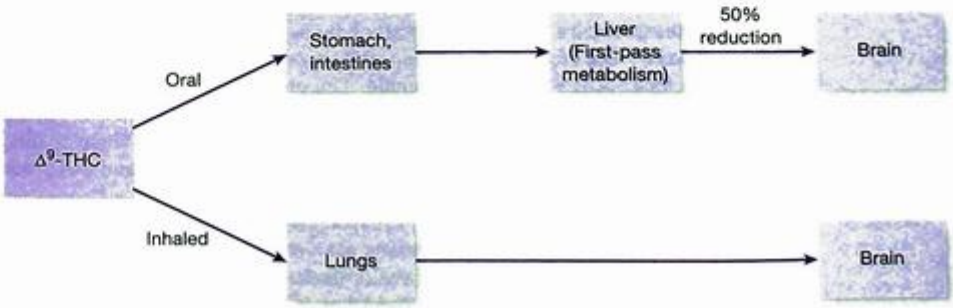
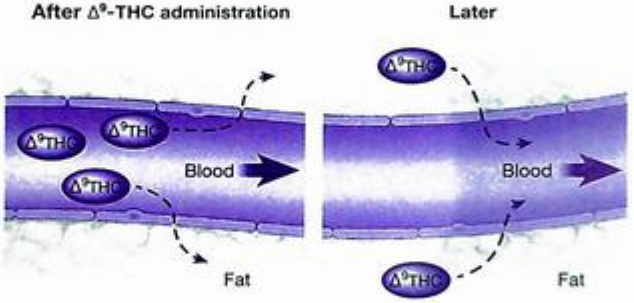


**FIGURE 11.2** **$\Delta^9$-THC Accumulation in Fat**

$\Delta^9$-THC molecules accumulate in fat after administration (left), leading to a later release of $\Delta^9$-THC into the bloodstream (right).




## Cannabinoid Compounds and the Endocannabinoid System

**Endocannabinoids**
Endogenous neurotransmitters, including anandamide and 2-AG, that activate cannabinoid receptors

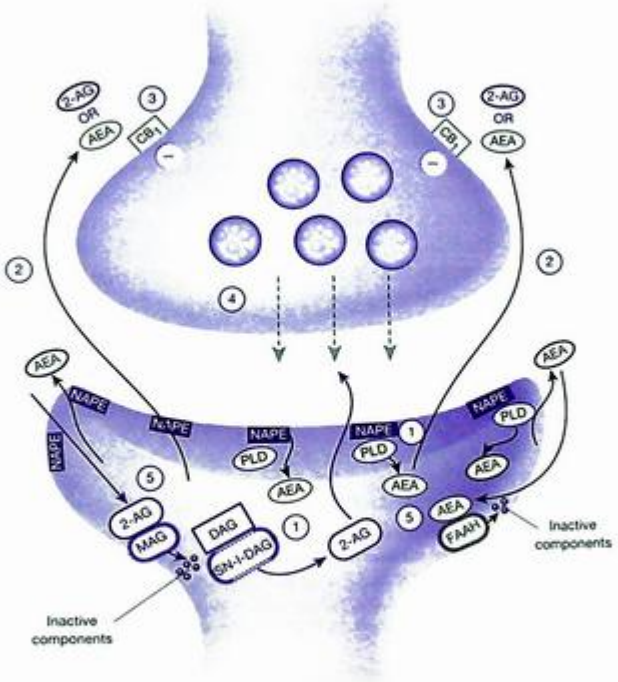
The effects of $\Delta^9$-THC and other psychoactive cannabinoid compounds occur by their actions on the endocannabinoid neurotransmitter system. **Endocannabinoids** are endogenous (derived internally) neurotransmitters that activate cannabinoid receptors. The first discovered was arachidonoyl ethanolamide, which was named *anandamide*, meaning "internal bliss" (Wiley, 1999). Another endocannabinoid is *2-arachidonoylglycerol* (2-AG).

**Figure 11.3** shows the process of neurotransmission for endocannabinoids. The production of anandamide and 2-AG comes through "on demand" biosynthesis—that is, synthesis occurs when needed rather than storing the molecules in vesicles for later release. The enzyme phospholipase D converts N-arachidonoyl-phosphatidylethanolamine (NAPE) into anandamide. The enzyme sn-1-diacylglycerol lipase converts a diacylglycerol to 2-AG. Synthesis of anandamide and 2-AG occurs in the *postsynaptic terminal*, and their release into a synapse allows them to bind to receptors on the *presynaptic terminal*. In this way, anandamide and 2-AG act as *retrograde neurotransmitters*.

Following receptor activation in the synapse, both anandamide and 2-AG return to the postsynaptic terminal via processes not yet fully determined. The enzyme fatty acid amide hydrolase (FAAH) breaks down anandamide into inactive components, and the enzyme monoacylglycerol lipase breaks down 2-AG into inactive components (Blankman, Simon, & Cravatt, 2007).

**FIGURE 11.3 Endocannabinoid Neurotransmission**

1) Anandamide (shown as AEA) is synthesized from NAPE through a NAPE-phospholipase D enzyme (PLD). 2-AG is synthesized from a diacylglycerol (DAG) by the enzyme sn-1-diacylglycerol lipase (sn-1-DAG). 2) Anandamide and 2-AG are released immediately after synthesis—there are no vesicles for these neurotransmitters. 3) Anandamide or 2-AG binds to $CB_1$ receptors on the presynaptic terminal. 4) When activated, the $CB_1$ receptor causes inhibitory effects, reducing release of neurotransmitters synthesized in the presynaptic neuron. 5) Breakdown of anandamide occurs by the enzyme FAAH and of 2-AG by the enzyme monoacylglycerol lipase (shown as MAG).




The various behavioral and physiological effects described for cannabinoids (e.g., $\Delta^9$-THC) and endocannabinoids (e.g., anandamide) result from actions at **cannabinoid receptors**. Two such receptors have been confirmed and thoroughly studied: the cannabinoid $CB_1$ and $CB_2$ receptors. Both receptors are G-protein-coupled receptors that exhibit inhibitory effects.

**Cannabinoid receptors**
G-protein-coupled receptors consisting of $CB_1$ and $CB_2$ activated by cannabinoids

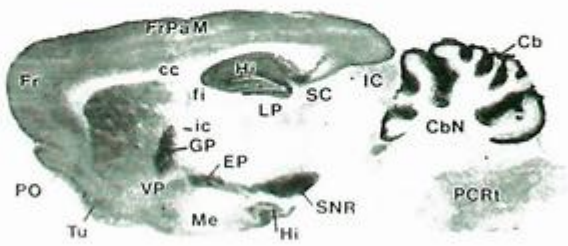
In the brain, $CB_1$ receptors densely occur in the basal ganglia, nucleus accumbens, substantia nigra, cerebellum, hippocampus, and cerebral cortex. $CB_1$ receptors also are found in the hypothalamus, in the thalamus, and throughout the brain stem (**Figure 11.4**) (Herkenham et al., 1990). A dense population of $CB_1$ receptors also exists in the eye, which may potentially play a role in cannabis-induced reductions of intraocular pressure, discussed later in this chapter (Porcella, Casellas, Gessa, & Pani, 1998; Porcella, Maxia, Gessa, & Pani, 2000). Outside the brain, $CB_1$ receptors can be found in the heart, kidneys, liver, spleen, and intestines. With the exception of glial cells, $CB_2$ receptors reside outside of the brain, particularly in the immune system on leukocytes (including B cells, natural killer cells, and T cells), and mast cells (important for injury response) (Brown, 2007; Munro, Thomas, & Abu-Shaar, 1993).

Cannabinoid compounds vary in their affinity for $CB_1$ and $CB_2$ receptors, which can account for their different potencies for eliciting pharmacological effects. **Table 11.3** shows the receptor affinities for selected cannabinoid compounds (see Box 2.1 for a review of receptor-binding procedures). For the endocannabinoids, anandamide exhibits a high affinity for $CB_1$ receptors and a lower affinity for $CB_2$ receptors, whereas 2-AG exhibits a weak affinity for both types of receptors. Among the cannabinoids found in cannabis, $\Delta^9$-THC exhibits high affinities for $CB_1$ and $CB_2$ receptors. Cannabinol has a moderate affinity for $CB_1$ receptors and weak affinity for $CB_2$ receptors, and cannabidiol has a negligible affinity for both types of receptors. The synthetic cannabinoids WIN52212-2, JWH-018, and JWH-073 exhibit similarly high affinities for $CB_1$ receptors and $CB_2$ receptors as $\Delta^9$-THC (Shoemaker et al., 2005; Thomas et al., 1998).

## FIGURE 11.4 Distribution of $CB_1$ Receptors in the Brain

Shown in a sagittal section of a rat brain, the darker portions are the result of higher levels of radioactivity from radiolabeled $CB_1$ receptors. Thus, the darker portion represents higher densities of $CB_1$ receptors, and the lighter portion represents lower densities of $CB_1$ receptors.

KEY (anterior to posterior): Fr = frontal cortex, FrPaM = motor cortex area, PO = Preoptic area, Tu = olfactory tubercle, cc = corpus callosum, VP = ventral pallidum, fi = fibria of the hippocampus, ic = internal capsule, GP = globus pallidus, EP = exterior pallidus, Me = median eminence, Hi = hippocampus, LP = lateral posterior thalamic nucleus, SC = superior colliculus, SNR = substantia nigra, CbN = cerebellar nuclei, Cb = cerebellum, PCRt = parvicellular reticular nucleus.




*Source:* Miles Herkenham, NIMH.

**TABLE 11.3** $CB_1$ and $CB_2$ Receptor Binding Affinities for Selected Cannabinoid Compounds

| Compound | Source | $CB_1$ Receptor Binding Affinity* | $CB_2$ Receptor Binding Affinity* |
|---|---|---|---|
| $\Delta^9$-THC (delta-9-tetrahydrocannabinol) | Main psychoactive component in cannabis | 5 | 3 |
| Cannabinol | Component in cannabis | 301 | 1130 |
| Cannabidiol | Component in cannabis | 2283 | 4200 |
| JWH-018 | Synthetic $CB_1$ receptor agonist used for research purposes and abused as a synthetic cannabinoid | 1.22 | 5.6 |
| JWH-073 | Synthetic $CB_1$ receptor agonist used for research purposes and abused as a synthetic cannabinoid | 12.9 | 9.8 |
| WIN52212-2 | Synthetic $CB_1$ receptor agonist used for research purposes and abused as a synthetic cannabinoid | 9.9 | 0.29 |
| Anandamide | Endocannabinoid neurotransmitter | 30 | 1940 |
| 2-AG | Endocannabinoid neurotransmitter | 1750 | 1016 |

*Expressed as Ki (nM Concentration)—recall that lower Ki values represent high affinities for receptors.

*Sources:* Data from Brents et al. (2011); Brents et al. (2012); Felder et al. (1995); Rajasekaran et al. (2013); Iwamura et al. (2001); Shoemaker et al. (2005); Thomas et al. (1998); Thomas et al. (2007).

Given the negligible affinity of cannabidiol for $CB_1$ and $CB_2$ receptors, researchers generally describe it as a non-psychoactive substance. Yet, this does not mean that cannabidiol lacks activity in the central nervous system; in fact, cannabidiol acts on numerous receptors and other signalling proteins, leading some researchers to refer to it as a "multi-target drug" (Devinsky et al., 2014). One of these actions includes antagonism of *GPR55*, a G-protein-coupled receptor thought at one time to be a third type of cannabinoid receptor. GPR55 regulates food intake and, if activated, might increase feelings of hunger and lead to weight gain (Liu, Song, Jones, & Persaud, 2015). Cannabidiol also promotes activity of the $5\text{-HT}_{1A}$ receptor, which as noted in Chapter 14, may play a role in anxiety. Cannabidiol exhibits a negligible affinity for

5-$HT_{1A}$ receptors, but instead, acts on intracellular mechanisms that become active when agonists bind to 5-$HT_{1A}$ receptors (Russo, Burnett, Hall, & Parker, 2005). Other pharmacological action that cannabidiol exhibits includes acting on glycine receptors and various transporters and ion channels (Devinsky et al., 2014).

Activation of $CB_1$ receptors leads to increased dopamine concentrations in the nucleus accumbens, as has been shown with WIN52212-2 using microdialysis procedures (Polissidis et al., 2012). $CB_1$ receptor agonists may act on $CB_1$ receptors on dopamine neurons in the ventral tegmental area or indirectly influence dopamine neuron activity by acting on $CB_1$ receptors located on glutamate or GABA neurons.

## STOP & CHECK

1. What are the two primary endocannabinoid neurotransmitters?
2. What effect might an FAAH inhibitor have if someone also was using cannabis?
3. Activation of $CB_1$ receptors causes _____ effects on the activity of a neuron.

1. anandamide and 2-AG 2. The FAAH inhibitor would likely enhance the effects of cannabis through increasing levels of the endocannabinoid anandamide. 3. inhibitory

## Physiological Effects of Cannabinoids

Given the wide reach of the endocannabinoid system, cannabinoid compounds exhibit many physiological effects. Acute administration of $\Delta^9$-THC causes a significant elevation in heart rate, and acute cannabis use is associated with hypotension and heart palpitations (Malit et al., 1975). Cannabis also produces a reddening of *conjunctivae*, the membrane covering the front of the eye and lining the inside of the eyelids. Redness comes from swelling of small blood vessels, which include the small blood vessels found at the bottom of the eye and membranes around the eye. Thus, we find cannabis associated with red or bloodshot eyes. $\Delta^9$-THC itself appears to exhibit minimal effects on respiration at the usual amounts administered. Many of the respiratory problems associated with cannabinoids occur from smoked preparations, as described later in the chapter (Battista et al., 2012).

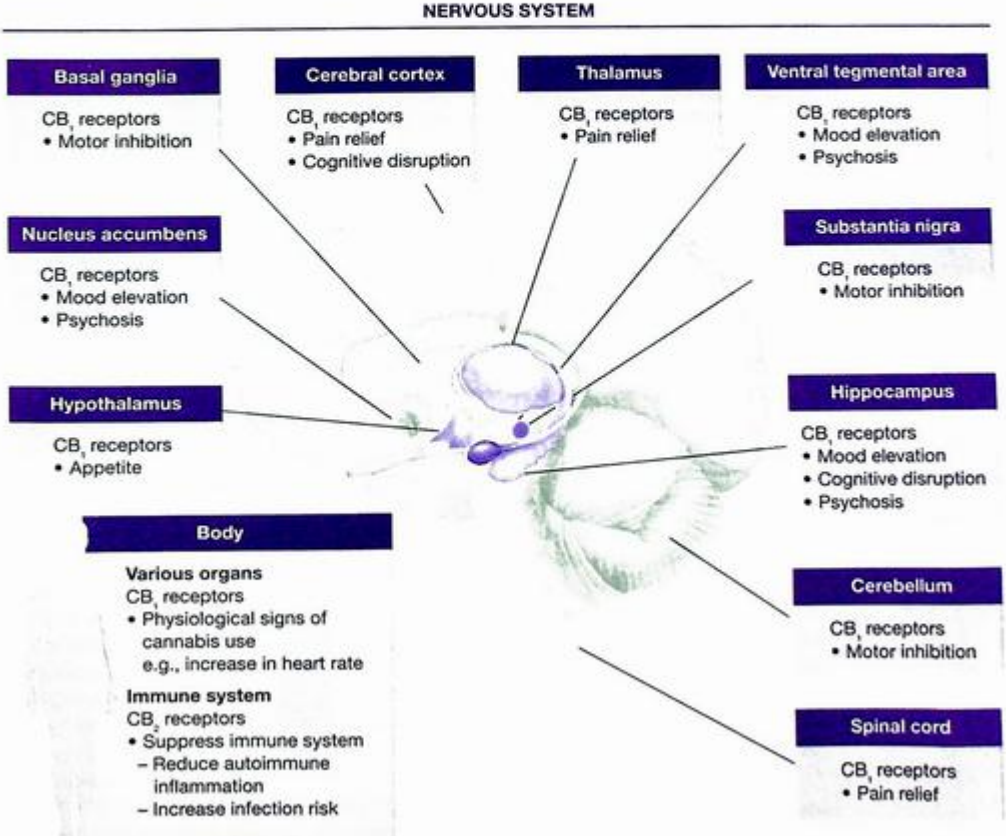
Cannabis use produces an increase in appetite, which recreational users refer to as having the "munchies." This is not a uniquely human phenomenon. For example, increased food intake is observed in *Hydra*, a tubular freshwater species that measures only a few millimeters long, after administration of the endocannabinoid anandamide (De Petrocellis, Melck, Bisogno, Milone, & Di Marzo, 1999). In rats, administration of anandamide leads to increased overnight food intake (Williams & Kirkham, 1999).

The endogenous cannabinoid system may be important for normal regulation of food intake. This inference is based on the effects that leptin, a *satiety hormone* (i.e., reduces hunger), has on anandamide and 2-AG release. After fat cells release

leptin, leptin reduces anandamide and 2-AG concentrations in the hypothalamus (**Figure 11.5**). When comparing obese versus lean laboratory mice, obese mice exhibit greater levels of anandamide and 2-AG in the hypothalamus, suggesting that lower endocannabinoid levels reduce food intake and greater endocannabinoid levels increase food intake. We find $CB_1$ receptors important for these effects, given that administration of a $CB_1$ receptor antagonist, SR141716A, reduces food intake

**FIGURE 11.5** **Locations and Effects for $CB_1$ and $CB_2$ Receptors**

The psychological and physiological effects of cannabinoids depend on the locations and function impact of $CB_1$ and $CB_2$.



in mice and that $CB_1$ receptor knockout mice consume less food than wild-type mice (**Figure 11.6**) (Di Marzo et al., 2001).

**Review!** The hypothalamus maintains many physiological processes through motivating an organism's behavior, such as producing hunger to motivate feeding (Chapter 2).

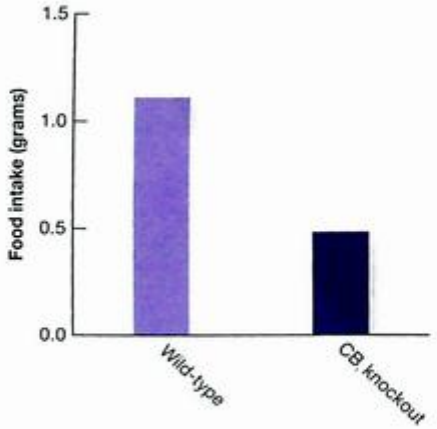
## STOP & CHECK

1. What causes red eyes from cannabis use?
2. Given that cannabis is an appetite enhancer, what therapeutic uses might the cannabinoid receptor antagonist offer?

1. Cannabis causes small blood vessels in the conjunctivae of the eye to swell, giving a red appearance. 2. If cannabis, which acts as an agonist for cannabinoid receptors, increases appetite, then a cannabinoid receptor antagonist might decrease appetite. In fact, researchers have assessed cannabinoid receptor antagonists as weight loss medications.

**FIGURE 11.6** **$CB_1$ Receptor Knock-Out Mice Have Reduced Appetites**

Reduced food intake occurs in $CB_1$ receptor knock-out mice (i.e., mice devoid of $CB_1$ receptors) compared to wild-type mice (i.e., mice with normal expression of $CB_1$ receptors) following 18 hours of food deprivation.




Source: Adapted from Di Marzo et al. (2001).

## Behavioral and Cognitive Effects of Cannabinoids

Many studies find mild memory deficits occurring after acute administration of cannabis or $\Delta^9$-THC. For example, Weil, Zinberg, and Nelsen (1968) found that, among human volunteers, cannabis use impaired memory performance while failing to impair attention performance. Curran, Brignell, Fletcher, Middleton, and Henry (2002) found that 15 mg of $\Delta^9$-THC, approximating moderate-potency marijuana, reduced both memory and attention. Deficits in memory and executive function occurred for higher amounts. In a study that sought to assess high-potency marijuana, Ramaekers and colleagues (2006) demonstrated deficits in memory, executive functioning, and psychomotor control following 35 mg of $\Delta^9$-THC.

In an attempt to trace neurobiological changes from cannabis use and effects on memory, Jager and colleagues (2006) conducted fMRI scans in frequent cannabis users and found lower functional activity in the hippocampus and dorsolateral prefrontal cortex, two structures linked to memory function, compared to control participants. Preclinical studies reveal extensive interactions of $CB_1$ receptor activation with firing rates, inhibition of long-term potentiation and depression formation (two processes important for memory; see Chapter 12), and decreased concentrations of the neurotransmitters acetylcholine and GABA in the hippocampus. Further, glutamate neurons from the hippocampus release less glutamate in other structures (Sullivan, 2000). The neurobiological findings overall suggest a disruption in hippocampal functioning that may lead to impaired memory.

The impact that cannabinoids have on neurobiological functions raises questions about the effects of cannabinoids on development, particularly concerning cognitive functioning. Numerous correlational studies have reported associations between cannabis use during adolescence and poorer academic performance and likelihood to remain in school (Lynskey & Hall, 2000). To examine cognitive performance, Harvey, Sellman, Porter, and Frampton (2007) evaluated adolescents who reported regular use of cannabis compared to those who did not. Participants received cognitive tests after they remained abstinent from cannabis for at least 12 hours. Across a variety of cognitive performance measures, the researchers found cannabis users to have lower IQ, poorer working memory, and slower information processing.

A challenge with studies like these is the question of whether or not study participants using cannabis inherently have these deficits, perhaps existing before cannabis use began. In an attempt to understand if cannabis use may lead to deficits or if the deficits already exist, Meier and colleagues (2018) conducted a longitudinal study among a sample of adolescents who were assessed for IQ when they were children. These authors found that lower IQ and poorer executive functioning occurred among older adolescents (age 18) who used cannabis, and that the decline in IQ positively correlated with the frequency of cannabis use (as previous studies also found). Yet, when comparing IQ scores at 18 years to scores as children, IQ scores had not changed. In other words, lower IQ values were apparent before cannabis use began.

$\Delta^9$-THC concentrations equivalent to moderate-potency marijuana also increase suspiciousness and paranoia, although the degree of these behaviors varies across individual users (Morrison et al., 2009). Yet, among those who have paranoid thoughts

from time to time, cannabis is especially likely to induce paranoia, something that Freeman and colleagues (2014) found by having study participants rate their perceptions of computerized characters they engaged with in a virtual environment. Psychotic effects also occur from use of synthetic cannabinoids (Every-Palmer, 2011). The prevalence of high-potency marijuana in recent years has provided additional concerns for the development of chronic psychotic disorders. Among these concerns is the diminishing ratio of cannabidiol to $\Delta^9$-THC, as cannabidiol has been viewed as a compound in cannabis that might ward against developing a neuropsychiatric disorder, such as schizophrenia (Pierre, 2017).

The ability of cannabis to produce paranoia and suspiciousness has given rise to the notion that cannabis use causes schizophrenia. Propaganda media, like the movie (and cult favorite) *Reefer Madness*, have claimed risks for psychosis from cannabis use for decades. Correlational studies have led to a general consensus that repeated cannabis use during adolescence is a risk factor for schizophrenia (Andréasson, Engström, Allebeck, & Rydberg, 1987; Manrique-Garcia et al., 2012). Moreover, those at strong risk of developing schizophrenia, such as having a history of paranoia or familial genetic risk, may be especially vulnerable, given that those at risk of schizophrenia experience stronger degrees of psychotic-like effects from acute use of cannabis (Vadhan, Corcoran, Bedi, Keilp, & Haney, 2017). Determining the nature of this risk, however, involves deciphering complex interactions between a genetic risk for schizophrenia (see Chapter 15), brain maturation during adolescence, and psychological factors, such as stress.

Cannabis tends to impair motor coordination and muscle tone. These effects, coupled with cannabis-induced impairments in reaction time, likely contribute to impaired driving ability and an increased number of auto accidents (Ramaekers, Berghaus, van Laar, & Drummer, 2004). These effects directly relate to the concentration of $\Delta^9$-THC and coincide with the subjective effects described as being *stoned* (Chesher, Bird, Jackson, Perrignon, & Starmer, 1990). Animal studies suggest that motor effects may change depending on the dose. In laboratory rats, low doses of $CB_1$ receptor agonists increase locomotor activity, whereas higher doses decrease locomotor activity (Polissidis et al., 2012).

**Amotivational syndrome**
Lack of motivation to engage in productive activities possibly related to cannabis use

McGlothlin and West (1968) first proposed an **amotivational syndrome** occurring in cannabis users. They characterized an amotivational syndrome as a persisting lack of motivation to engage in productive activities. Individuals with amotivational syndrome exhibit apathy, lethargy, and passivity that are manifested as a failure to follow through on long-term plans, an indulgence in childlike thinking, and an engagement in introversive behavior.

Despite these observations, many researchers have failed to confirm an amotivational syndrome in controlled laboratory settings. Several studies have tested the hypothesis that cannabis use should reduce the effectiveness of reinforcers if it reduces motivation. For example, if an individual loses interest in working, then one may reason that the individual has less motivation to earn money.

Published studies that investigated this hypothesis either reveal no effects on motivation or, in fact, find an increase in motivation. For example, Foltin and colleagues (1990) asked volunteers to live in a laboratory environment for two weeks and engage in various activities of low or high effort to earn reinforcers. In this study,

a *reinforcer* was an opportunity to conduct a task an individual preferred more than the one he or she was currently conducting. On certain days, participants smoked cannabis cigarettes (containing 2.7 percent $\Delta^9$-THC), but they smoked placebo cigarettes, which lacked $\Delta^9$-THC, on other days. The researchers reasoned that study participants would express amotivation by choosing less-effortful tasks. Yet when participants smoked the cannabis cigarettes, they actually chose the tasks requiring more effort. Thus, an amotivational syndrome was not apparent. The researchers instead concluded that smoking cannabis made effortful tasks seem less effortful.

A more recent study sought to further investigate the effects of cannabis on motivation. Lawn and colleagues (2016) assessed the effects of a vaporized solution containing $\Delta^9$-THC (8 mg/kg—equivalent to low-potency marijuana) with or without cannabidiol in human participants engaged in tasks with varying difficulty. In this study, participants given only $\Delta^9$-THC were significantly less likely to engage in effortful tasks compared to those given the combination of $\Delta^9$-THC with cannabidiol or compared to those given placebo. Thus, this study supports an amotivation effect from $\Delta^9$-THC when cannabidiol is absent and suggests that high-potency marijuana, which has a relatively low concentration of cannabidiol compared to $\Delta^9$-THC, is likely to reduce motivation.

## STOP & CHECK

1. What effects does cannabis use have on memory?
2. What is the hypothesis that many researchers test when investigating a potential amotivation syndrome for cannabis use?

1. Cannabis tends to impair memory. 2. Researchers sometimes assess the effectiveness of reinforcers, reasoning that a user finding a goal less reinforcing would therefore demonstrate reduced motivation.

## Subjective Effects of Cannabinoids

The subjective effects of cannabinoids are dose dependent. After a few puffs of marijuana, a user may experience a light-headed, dizzy feeling referred to as a *buzz*. A person with a buzz may also experience tingling sensations in the body. A *high* occurs after additional inhalations and is defined as a euphoric and exhilarating feeling. Increased agitation or anxiety is occasionally reported during the buzz and high phases as well. The *stoned* phase occurs with further usage and is described as a calm and relaxed state. This stage is also consistently characterized by **accelerated time**, a perceived faster passage of time, as described previously (Abood & Martin, 1992).

**Accelerated time** Perceived faster passage of time associated with cannabis use

Accelerated time appears to be related to the effects of cannabis on the cerebellum. In a positron emission tomography (PET) imaging study, Mathew and colleagues (1998) used PET to image cerebral blood flow following the administration of $\Delta^9$-THC in human participants. Although findings varied among the

participants, those who overestimated time passage exhibited reductions in blood flow to the cerebellum.

**Review!** The cerebellum facilitates balance and the timing of movements (Chapter 2).

To carefully assess the subjective effects of cannabis in humans in a laboratory environment, Curran and colleagues (2002) recruited 50 volunteers who had used cannabis in the past to rate how they felt after oral administration of $\Delta^9$-THC. The investigators chose both a low dose (7.5 mg/kg) and a high dose (15.0 mg/kg) of $\Delta^9$-THC to study, along with a placebo. Researchers employed a double-blind design so that neither the investigators nor the participants knew who received treatments during the study. The participants reported the strongest drug effect when given the highest dose of $\Delta^9$-THC. They liked both the low and high dose of $\Delta^9$-THC equally well, and they liked both of those more than the placebo. Similarly, they indicated a desire for more of the drug. The highest dose caused the most reports of being stoned, and the participants indicated difficulty remembering things.

Although this study employed oral administration of $\Delta^9$-THC, rather than smoked cannabis, the effects are likely similar. In a study conducted by Hart and colleagues (2002), experienced cannabis smokers reported similar subjective effects, including similar "high" and "stoned" effects between smoked cannabis and oral $\Delta^9$-THC. These findings further implicate $\Delta^9$-THC in the subjective effects of cannabis.

Drug discrimination studies can be used to study subjective effects in humans as well. In a study conducted by Lile, Kelly, Pinsky, and Hays (2009), the ability to discriminate between a specific dose of a training drug—in this case, 25 mg of $\Delta^9$-THC—and a compound with no drug effects (i.e., a placebo) were assessed in experienced cannabis users. The participants were given the drug or placebo orally, using pills that were identical in both appearance and taste. In fact, the participants were not even told that the training drug was $\Delta^9$-THC; rather, they were told to closely attend to effects experienced after taking "drug X." The human participants then rated, by repeatedly clicking "drug" or "no drug" on a computer screen, their certainty that they had received drug X. After attaining a high level of accuracy, researchers administered a different test substance to the participants. **Figure 11.7** shows the results from this study. Participants clicked for drug X after $\Delta^9$-THC administration and they seldom clicked for drug X after administration of a benzodiazepine, opioid, or psychostimulant drug. Thus, the stimulus effects of $\Delta^9$-THC appear different from those produced by these other drug classes.

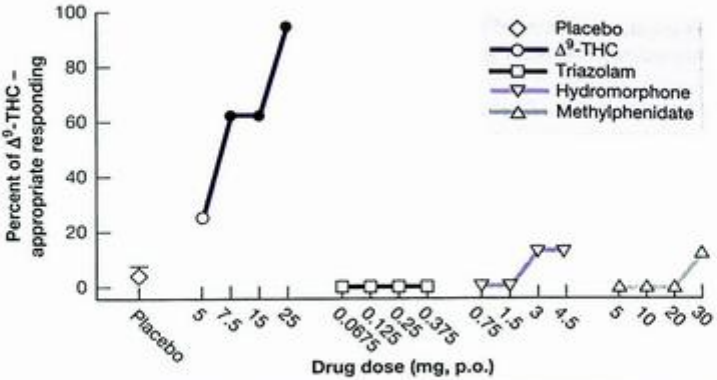
## STOP & CHECK

1. What are the dose-dependent phases of the subjective effects of cannabis?
2. Which brain structure may be responsible for the perception of accelerated time during cannabis use?

1. As the dose increases, an individual will experience buzzed, high, and stoned phases. 2. cerebellum

**FIGURE 11.7 Stimulus Properties of Δ⁹-THC in Human Participants**

In humans trained to discriminate Δ⁹-THC versus placebo in a drug discrimination task, only Δ⁹-THC produced Δ⁹-THC-appropriate responding, whereas drugs from other classes did not.




*Source:* With kind permission from Springer Science+Business Media: Lile, J. A., Kelly, T. H., Pinsky, D. J., & Hays, L. R. (2009). Substitution profile of Delta9-tetrahydrocannabinol, triazolam, hydromorphone, and methylphenidate in humans discriminating Delta9-tetrahydrocannabinol. *Psychopharmacology* (Berl), 203(2), 241, p. 10.

## Cannabis Use Disorder

**Cannabis use disorder**
Defined by the DSM-5 as cannabis use meeting the criteria for a substance use disorder

**Cannabis withdrawal syndrome**
Occurrence of physical and psychological withdrawal symptoms in the absence of cannabis

The *Diagnostic and Statistical Manual* (DSM-5) describes a **cannabis use disorder** as meeting the general criteria for a substance use disorder, as first presented in Chapter 5 (American Psychiatric Association, 2013a). Features include using more cannabis than originally intended; cravings; and replacing normal, healthy activities with cannabis use, among others. Approximately nine percent of adults who use cannabis develop cannabis use disorder (Anthony, Warner, & Kessler, 1994).

Further, the DSM-5 recognizes tolerance developing during cannabis use and describes a **cannabis withdrawal syndrome** as including irritability, anger, aggression, anxiety, difficulty sleeping, decreased appetite, and depressed mood as well as any physical withdrawal symptoms, such as stomach pain, tremor, sweating, headache, or fever. Regular cannabis users find tolerance to many of cannabis's behavioral and subjective effects, including memory impairment, motor coordination, and accelerated time passage (Abood & Martin, 1992). However, tolerance more readily develops to high doses of Δ⁹-THC. Gorelick and colleagues (2013) evaluated four daily escalating doses of oral-administered Δ⁹-THC among regular cannabis smokers. The daily dose on day one consisted of 40 mg, days two through four consisted of 100 mg, and days five and six consisted of 120 mg. At these higher doses, subjective effects of Δ⁹-THC, such as feeling stoned, experiencing good effects, and a high, increased by day two, but had declined by day six, despite receiving the highest doses on days five and six.

## Health Risks of Cannabis

Although cannabis presents some possible medical benefits for cancer, cannabis cigarettes share a number of carcinogens with tobacco cigarettes. These carcinogens include benzanthracene and benzpyrene compounds. In fact, cannabis cigarettes contain greater amounts of these chemicals than do tobacco cigarettes. Compared to tobacco, cannabis smoking results in greater amounts of tar in the lungs (Ashton, 2001).

Despite sharing similar carcinogen content with tobacco, cannabis smoke also yields different chemicals that may limit a user's risk for lung cancer. This may explain why correlational studies fail to find increased risk of lung cancer among cannabis smokers (Hashibe et al., 2005; Mehra, Moore, Crothers, Tetrault, & Fiellin, 2006). Moreover, cannabis contains compounds that may reduce cancers of the skin, breast, and prostate, suggesting that these compounds may counteract the carcinogens found in cannabis (Melamede, 2005). Aside from cancer risk, cannabis smoking may increase the risk of respiratory diseases such as bronchitis and emphysema, although this risk increases most for users who smoke both cannabis and tobacco (Ashton, 2001; Tan et al., 2009). Other adverse effects may derive from the preparation of the cannabinoid or its manner of use. One of the more common significant adverse effects reported from use of synthetic cannabinoids is damage to kidneys (Centers for Disease Control and Prevention, 2013).

## STOP & CHECK

1. How are some withdrawal effects from cannabis related to the drug effects of cannabis?
2. Although cannabis tar contains carcinogens, why might cancer risk not be evident in correlational studies?

1. Some withdrawal effects appear as compensatory effects from cannabis use. Thus, the withdrawal effect of *reduced appetite* is the result of compensating for the *appetite enhancement* of cannabis. Other withdrawal effects can be linked to the drug effects of cannabis in this way. 2. Unlike tobacco tar, cannabis tar includes chemicals that might reduce cancer risk, potentially compensating for the effects of carcinogens in some way. Still, there's much to learn about cancer risk and cannabis smoking before one can state with certainty the safety of cannabis products in this regard.

## From Actions to Effects: Medical Use of Cannabinoids

Although marijuana is a popular recreational substance, cannabis has become well-known for medicinal effects. When investigating the scientific validity of using marijuana as a medical treatment, researchers study both the effects of cannabis and the effects of phytocannabinoids. In particular, $\Delta^9$-THC and cannabidiol have received the most scientific support for garnering therapeutic effects for selected conditions.

Amid a number of purported uses, evidence mainly supports **medicinal cannabis** for managing cancer medications, unhealthy weight loss, pain, intraocular pressure, and autoimmune diseases (**Table 11.4**) (Alexander, 2016).

**Medicinal cannabis**
Cannabis used for treating medical conditions such as cancer, weight gain, pain, intraocular pressure, and autoimmune diseases

For the treatment of cancer, cannabis may help patients cope with adverse side effects of *chemotherapy*, the use of medicines that kill rapidly dividing cells. In 1985, the Food and Drug Administration (FDA) approved the prescription of $\Delta^9$-THC, again known as dronabinol (*Marinol*), for the reduction of nausea and vomiting during chemotherapy. However, with the development of other medications for treating chemotherapy-induced nausea and vomiting, physicians usually do not prescribe dronabinol as a first-line treatment (Todaro, 2012). Cannabis' well-known appetite-enhancing effects also make it useful for promoting weight gain for conditions that diminish appetite, including cancer, chemotherapy treatment, and HIV infection. We find these effects with dronabinol in another approved drug chemically similar to $\Delta^9$-THC, *nabilone* (*Cesamet*) (Haney et al., 2007; Turcott et al., 2018).

Only tentative evidence exists in clinical trials to suggest that medical marijuana may effectively treat cancer. In one study, physicians injected $\Delta^9$-THC directly into glioblastoma multiforme tumors (a type of brain tumor) and found evidence of temporary reductions in tumor progression (Guzmán et al., 2006). Other than this, most evidence for using cannabinoids as cancer treatment comes from studies in animals and using tumor cells (Massi, Solinas, Cinquina, & Parolaro, 2013).

Ellis and colleagues (2009) found that smoked cannabis significantly reduces neuropathic pain in HIV-infected patients compared to placebo control. These findings coincided with findings by Ware and colleagues (2010) that smoked cannabis reduces neuropathic pain in patients after suffering a trauma or when recovering from surgery. The pain-relieving properties of cannabinoids may result from activation of $CB_1$ receptors in the thalamus, brain stem, and cerebral cortex. Moreover, $CB_1$ receptors are located on neurons within the spinal cord where cannabinoids may reduce pain signalling to the brain (Pertwee, 2001).

**TABLE 11.4 Medical Uses for Cannabis**

| Disorder | Effects of Cannabis |
|---|---|
| Autoimmune disease | Inhibits immune system functioning; appears effective for multiple sclerosis |
| Cancer | Reduces nausea and vomiting associated with chemotherapy; limited evidence showing reduced tumor growth in patients |
| Epilepsy | Reduces frequency of seizures, especially with cannabidiol alone or for high cannabidiol concentration in cannabis |
| Glaucoma | Relieves intraocular eye pressure |
| Neuropathic pain | Reduces neuropathic pain from trauma or surgery |
| Unhealthy weight loss | Promotes weight gain in disorders that diminish appetite |

Cannabis and phytocannabinoids may offer therapeutic benefits for glaucoma, a disease characterized by damage to the optic nerve from increased fluid pressure in the eye. Hepler and Frank (1971) first reported that smoking cannabis cigarettes led to a significant reduction in intraocular pressure. Several studies reported that $\Delta^9$-THC engendered similar effects (Merritt, Crawford, Alexander, Anduze, & Gelbart, 1980; Purnell & Gregg, 1975). Porcella, Maxia, Gessa, and Pani (2001) also found that a selective $CB_1$ receptor agonist WIN52212-2 significantly reduced intraocular pressure in patients, concluding that $CB_1$ receptors play a direct role in mediating fluid pressure in the eye.

Cannabinoids also suppress immune system functioning. These actions are illustrated in a survey of routine cannabis users in Italy and Spain conducted by Pacifici and colleagues (2003). Through analyzing blood drawn from these participants over the course of six months, self-reported cannabis use was associated with reduced numbers of natural killer cells as well as general suppressed activity among various immune system cells. This included a reduction in proinflammatory cytokines, as well as an increase in anti-inflammatory cytokines. Thus, cannabis may be effective medicinally for autoimmune inflammation, but cannabis use may also enhance one's risk of infection.

For multiple sclerosis, both $\Delta^9$-THC and cannabidiol reduced spasticity (i.e., continuous muscle contractions) and general motor function in animal models (Ayoglu et al., 2016; Feliú et al., 2015). In clinical trials, *Sativex*, a one-to-one ratio of cannabidiol and $\Delta^9$-THC, reduced spasticity among multiple sclerosis patients, although $\Delta^9$-THC alone did not. Overall, we find a general consensus that *Sativex* and $\Delta^9$-THC have some efficacy for multiple sclerosis (Alexander, 2016; Koppel et al., 2014). *Sativex* is currently approved in the United Kingdom, Spain, and Canada for the treatment of muscle spasms and stiffness in multiple sclerosis. Canada also approved *Sativex* for the treatment of pain in cancer. Patients indicate that *Sativex* is generally well tolerated (Barnes, 2006; Wade, 2012).

## Drug Profile: cannabidiol and $\Delta^9$-THC (1:1 ratio)

| | |
|---|---|
| Brand name | *Sativex* |
| Properties | Agonist for cannabinoid $CB_1$ and $CB_2$ receptors |
| Uses | Cannabinoid medication for the treatment of multiple sclerosis and cancer pain |

We find clinical evidence that cannabidiol serves as a treatment for seizures. One of the first studies to examine cannabidiol for epilepsy was conducted in 1980 by Cunha and colleagues, who found it to be effective and well tolerated. More recently, Devinsky and colleagues (2016) conducted a large open-label study among those with seizure disorders who did not respond adequately to traditional seizure medications

and found clinically significant reductions in seizures with an acceptable safety profile among those patients. In this study, patients that most commonly responded well to cannabidiol had either Dravet syndrome or Lennox-Gastaut syndrome. These findings also suggest an effectiveness for medical marijuana, but likely when the preparation comes from a strain with a high ratio of cannabidiol.

## STOP & CHECK

1. What is the FDA-approved use for dronabinol?
2. How might cannabis relieve glaucoma?
3. Why might cannabis users prefer smoking cannabis as opposed to taking dronabinol for medicinal purposes?

1. The FDA approved dronabinol for the reduction of nausea and vomiting during chemotherapy.
2. $CB_1$ receptors in the eye may have a direct role in fluid pressure. a contributor to optic nerve damage in glaucoma. $\Delta^9$-THC in cannabis may relieve this pressure by activating these $CB_1$ receptors.
3. First, smoking cannabis allows patients to adjust drug levels to achieve and maintain a desired effect. Second, other components in cannabis may counteract some of the negative subjective effects of dronabinol.

## CHAPTER SUMMARY

Cannabinoids represent a class of drugs that produces psychoactive effects by acting on cannabinoid receptors in the nervous system. Cannabinoids exist in cannabis plants, are produced as synthetic drugs, and occur as endogenous neurotransmitters. Cannabis plants produce psychoactive effects through $\Delta^9$-THC, their main psychoactive constituent. With the exception of prescription $\Delta^9$-THC (dronabinol), the DEA lists cannabinoid compounds as schedule I controlled substances. Users smoke or orally administer cannabinoid compounds. Once in the body, $\Delta^9$-THC has a long elimination rate, which increases during chronic cannabis use. Cannabinoid compounds engender pharmacological actions by acting on the endocannabinoid system, which involves neurotransmitters called anandamide and 2-AG that bind to $CB_1$ and $CB_2$ cannabinoid receptors. Cannabis use increases heart rate, enhances appetite, produces deficits in memory, and impairs motor coordination. The subjective effects include euphoria, relaxation, and overestimation of time passage. Regular use of cannabis results in tolerance to many of its pharmacological effects. There has been extensive research on the use of medical marijuana and cannabinoid compounds. In particular, cannabinoids may reduce adverse effects from chemotherapy, promote weight gain, relieve pain, reduce intraocular pressure, treat certain autoimmune diseases, and reduce seizures.

# KEY TERMS

Cannabinoids 352
Cannabis 352
Phytocannabinoids 352
$\Delta^9$-tetrahydrocannabinol ($\Delta^9$-THC) 352
Marijuana (or marihuana) 352
Dabbing 353
Hashish 353
Synthetic cannabinoids (or synthetic marijuana) 353
Liquid incense (or cannabinoid-enhanced electronic liquid) 354
Contact high 358
Endocannabinoids 360
Cannabinoid receptors 361
Amotivational syndrome 368
Accelerated time 369
Cannabis use disorder 371
Cannabis withdrawal syndrome 371
Medicinal cannabis 373

CHAPTER 12

# Psychedelic Drugs

## Chapter Outline

- Hallucinogens
- Mixed Stimulant–Psychedelic Drugs
- Dissociative Anesthetics
- Other Psychedelic Drugs
- From Actions to Effects: Synesthesia

## Learning Objectives

- Compare and contrast effects of different types of psychedelic drugs
- Examine the neurobiological mediators of psychedelic experiences
- Interpret the pharmacokinetic actions of psychedelic drugs in the context of their manner and reasons for use
- Evaluate the health risks of psychedelic use

**Psychedelic drugs** induce a reality-altering experience consisting of hallucinations, sensory distortions, or delusions. The term *psychedelic* means "mind expanding." Within this definition, we find a wide variety of pharmacological effects among psychedelic substances. For this reason, we further classify psychedelic drugs into three general categories: *hallucinogens, mixed stimulant–psychedelics,* and *dissociative anesthetics.* This chapter will focus on the representative drugs for each category, including the hallucinogen *LSD* (*acid*), the mixed stimulant–psychedelic *MDMA* (*Ecstasy*), and the dissociative anesthetic *phencyclidine* (*PCP*) (Abraham, McCann, & Ricaurte, 2002). Drugs that do not fit well into these categories are covered at the end of the chapter.

**Psychedelic drugs**
Drugs that induce a reality-altering experience consisting of hallucinations, sensory distortions, or delusions

## Hallucinogens

**Hallucinogens**
Large class of psychedelic drugs that produces hallucinations as its main pharmacological effect

**Lysergic acid diethylamide (LSD)**
A representative hallucinogenic drug

**Hallucinogens** represent a large class of psychedelic drugs that produces hallucinations as its main pharmacological effect. The most representative drug of this class is **lysergic acid diethylamide (LSD)**, well-known by the street name *acid* as well as a variety of other names. Other hallucinogens include psilocybin, mescaline, and dimethyltryptamine. LSD is synthesized from lysergic acid using any number of preparation methods (Soine, 1986). In response to these measures, the Drug Enforcement Administration (DEA) not only classified LSD as a schedule I controlled substance but also classified its precursor, lysergic acid, as a schedule I controlled substance (Drug Enforcement Administration, 2012b).

### Drug Profile: lysergic acid diethylamide (LSD)

| | |
|---|---|
| Street name | *Acid*, among others |
| Subjective effects | Visual hallucinations |

**Psilocybin**
Main psychoactive constituent in hallucinogenic mushrooms belonging to the genus *Psilocybe*

**Psilocybin** is the main psychoactive constituent in hallucinogenic mushrooms belonging to the genus *Psilocybe* (Schultes, 1969). Users refer to these mushrooms by different street names such as *magic mushrooms* or *shrooms*. After oral administration, psilocybin rapidly converts to its active metabolite psilocin, a hallucinogenic substance that likely accounts for most of psilocybin's effects (Hasler, Bourquin, Brenneisen, Bar, & Vollenweider, 1997).

### Drug Profile: psilocybin (and psilocin)

| | |
|---|---|
| Street name | *Magic mushrooms*, among others |
| Subjective effects | Visual hallucinations; produced mostly from active metabolite, psilocin |

*Mescaline* is found in *peyote*, a small, spineless cactus native to southern North America (**Figure 12.1**). Users obtain mescaline by chewing disk-shaped buttons within the cactus crown (Schultes, 1969). Street names for mescaline include *peyote* (in reference to the plant), *buttons*, and *mesc*, among others. As noted in the next section, mescaline is used in some religious practices.

**FIGURE 12.1 The Peyote Cactus**

The peyote cactus contains the hallucinogen mescaline. Mescaline is concentrated in the "button"-shaped feature on the crown of the cactus.

Copyright iStockphoto/bob cheung

## Drug Profile: mescaline

| | |
|---|---|
| Street name | *Peyote*, among others |
| Subjective effects | Visual hallucinations; used in some religious ceremonies |

Another hallucinogen is **dimethyltryptamine (DMT)**. We find DMT in *Mimosa hostilis*, *Virola calophylla*, and other hallucinogenic South American plants (Agurell, Holmstedt, Lindgren, & Schultes, 1969). Plants containing DMT may be brewed to make a drink called *ayahuasca*. Unlike other hallucinogens, the brain produces small amounts of DMT. The function of endogenous DMT remains largely unknown, although it appears to serve as an agonist for sigma-1 receptors (Angrist et al., 1976; Axelrod, 1961; Fontanilla et al., 2009; Frecska, Szabo, Winkelman, Luna, & McKenna, 2013). The sigma-1 receptor was once considered a receptor for opioids, but subsequent research found sigma-1 as a site on the endoplasmic reticulum (Hayashi & Su, 2007). Further, DMT may act on the serotonin system, but these potential interactions have yet to be sorted out (Frecska et al., 2013). We find small concentrations released in the pineal gland, which has led to notions of DMT's role in vivid dreaming. However, this connection between DMT and vivid dreams is not well supported by scientific studies (Nichols, 2018).

**Dimethyltryptamine (DMT)**
Hallucinogenic compound found in certain South American plants and produced endogenously

## Drug Profile: dimethyltryptamine (DMT)

| | |
|---|---|
| Street name | *DMT*, among others |
| Action | Unknown, but may activate sigma-1 receptors and may act on the serotonin system |
| Subjective effects | Visual hallucinations; small amounts produced in the brain |

A newer class of hallucinogens is called *NBOMe drugs*, a reference to their chemical structure as N-methoxybenzyl, and they are molecular analogs of different families of phenethylamine compounds. Users typically refer to NBOMe drugs as "n-bombs." Their use mainly began in 2010, and many countries still have yet to regulate them. They produce pharmacological actions and effects similar to other hallucinogens, and their prevalence of use is currently regarded as low (Wood, Sedefov, Cunningham, & Dargan, 2015).

Overall, approximately nine percent of adults in the United States have used a hallucinogenic substance. Moreover, this survey found that many of those using hallucinogens had a mood disorder, in addition to another substance disorder, an eating disorder, or a type of personality disorder (Shalit, Rehm, & Lev-Ran, 2019). We find hallucinogen use not uncommon on college campuses. In surveys of college students, approximately six percent reported using a hallucinogenic substance (Allen et al., 2017).

## STOP & CHECK

1. What are the three main types of psychedelic drugs?
2. What is the representative drug for hallucinogens?
3. What is the hallucinogenic compound found in peyote?

1. hallucinogens, mixed stimulants–psychedelics, and dissociative anesthetics 2. lysergic acid diethylamide (LSD) 3. mescaline

### Origins of LSD and Other Hallucinogens

Ancient cultures used hallucinogenic plants as psychic medicines to treat maladies, communicate with gods, and perform magic. The Aztecs used peyote and similar hallucinogens in religious ceremonies. In addition to rich visual hallucinations, peyote granted perceptions of great insight and altered realities, providing the integral

experience of communicating with gods. The Spanish conquistadors banned these practices, but neither the Inquisitors nor military authorities eliminated peyote's ceremonial use (Schultes, 1969).

In the mid-18th century, peyote use was adopted by Native American cultures and was used in religious ceremonies by the Comanche, Kiowa, Cheyenne, and many other tribes. Comanche Chief **Quanah Parker** stated that the Great Spirit Within communicated with him through a peyote experience to make peace with the white man and seek spiritual communion and wisdom.

**Quanah Parker**
Comanche chief who advocated using peyote in religious ceremonies

When Oklahoma outlawed peyote in 1899, Quanah Parker helped persuade the state legislature to overturn the law, which it did in 1908. Peyote's legal status continued largely because of its importance to the Native American Church of North America. As the use of peyote continued in Native American groups, peyote use spread among U.S. college campuses during the 1950s and 1960s (Brecher, 1972). Today, peyote and its primary psychoactive ingredient mescaline are schedule I controlled substances, although this act exempts peyote use for religious purposes by the Native American Church of North America (U.S. Congress, 1994).

Hallucinogenic substances have existed in plants for as long as humans have existed. In fact, Caporael (1976) wrote a convincing case that the infamous Salem witchcraft trials occurred because of accidental exposure to ergot fungus among the residents. Swiss chemist **Albert Hofmann** accidentally discovered LSD's hallucinogenic effects at Sandoz Laboratories in 1943 while synthesizing derivatives from ergot.

**Albert Hofmann**
Swiss chemist who discovered LSD

On April 16, 1943, Hofmann had been mixing derivatives of ergot fungi and acquired a sudden illness, journaling later that he experienced a "great restlessness and mild dizziness" followed later by a pleasant delirium containing "extremely excited fantasies" along with "fantastic visions of extraordinary realness and with an intense kaleidoscopic play of colors" (Brecher, 1972). He deduced that an accidental exposure to something he prepared had occurred and the next day he took deliberately, as a self-experiment, a small amount of the 25th compound of Sandoz Laboratories' lysergic acid series, referred to as LSD-25.

Hofmann learned two key things from his self-experiment with LSD. The first was dosage. He took only one-quarter milligram of LSD, which to his surprise produced a strong effect. The second thing was that LSD is a powerful hallucinogenic drug. Hofmann's second "trip" lasted hours and wasn't as pleasant as his first experience. Hofmann's account of the experience goes as follows (Brecher, 1972):

> "As far as I can remember, the following were the most outstanding symptoms: vertigo, visual disturbances, the faces of those around me appeared as grotesque, colored masks; marked motoric unrest, alternating with paralysis; an intermittent feeling in the head, limbs, and the entire body, as if they were filled with lead; dry, constricted sensation in the throat; feeling of choking; clear recognition of my condition, in which state I sometimes observed, in the manner of an independent neutral observer, that I shouted half insanely or babbled incoherent words. Occasionally I felt as if I were out of my body. . . . Especially noteworthy was the fact that sounds were transposed into visual sensations so that from each tone or noise a comparable colored picture was evoked, changing in form and color kaleidoscopically."

After LSD's hallucinogenic effects were discovered, the substance was tested for a variety of uses. The U.S. Army tested LSD as an aid for inducing captured enemy prisoners to talk more freely. The army also tested LSD as a chemical weapon. During the psychoanalysis era, psychiatrists used LSD to gain access to supposedly unconscious thoughts in their patients (Brecher, 1972). Antony Busch and Warren Johnson (1950) published the first paper for LSD use in psychiatric patients, stating that LSD "may offer a means of more readily gaining access to the chronically withdrawn patients" and that its use might shorten psychotherapy. Other studies supported these claims (Chandler & Hartman, 1960; Natale, Kowitt, Dahlberg, & Jaffe, 1978).

In 1960, Sidney Cohen reported on a LSD survey returned by 44 researchers and therapists. These respondents reported administering LSD to nearly 5,000 men and women, equating to more than 25,000 total administrations. The volume of LSD therapeutic use declined, however, as published reports and conference proceedings noted negative psychological experiences, referred to as *bad trips*, emerging in many patients. Many practitioners especially feared producing prolonged bad trips, lasting as long as 48 hours. Occasionally, bad trips led to suicides.

**Harvard Psilocybin Project**
Studies led by Timothy Leary and Richard Alpert to examine effects of psilocybin in human volunteers

Psychologist Timothy Leary became a well-known figure among hallucinogen users after leading studies alongside Richard Alpert on the effects of psilocybin in human volunteers at Harvard University for what was referred to as the **Harvard Psilocybin Project** from 1960 to 1962. One of the founding board members included Aldous Huxley, who was famous for the novel *Brave New World* (1932) and his nonfiction accounts of his experiences taking mescaline in *The Doors of Perception* (1954). One of the Harvard Psilocybin Project studies, referred to as the *Concord Prison Experiment*, reported lower recidivism rates among paroled former inmates because of combined psilocybin treatment with psychotherapy (Leary et al., 1965). However, an account of this study later written by Ralph Metzner, a co-author of the original study, reported a fabrication of these data (Metzner, 1998). Another experiment, called the *Marsh Chapel Experiment*, found that psilocybin induced profound religious experiences among divinity students (Pahnke & Richards, 1966). Follow-up studies reported similar findings (Doblin, 1991).

State and federal regulations for LSD increased as therapeutic use of LSD decreased (Brecher, 1972). Eventually, LSD and other hallucinogens became schedule I controlled substances, precluding therapeutic use. Research on LSD and other hallucinogens in humans continues in order to learn about their pharmacological actions and, in some cases, to examine potential therapeutic uses.

## STOP & CHECK

1. Who discovered LSD's hallucinogenic effects?
2. Aside from recreation, what were the other historical uses of LSD?

1. Albert Hofmann, a chemist who worked for Sandoz Laboratories 2. LSD was tested by the U.S. military to aid in prisoner interrogation and to use as a chemical weapon. The drug was also used in psychotherapy.

## LSD Ingestion and Effects

LSD and most other hallucinogens are normally orally administered. This was the administration route used by Albert Hofmann's accidental LSD ingestion and self-experimentation described previously. LSD is potent, with effective amounts beginning at only 0.025 mg. Researchers consider 0.075 to 0.15 mg a moderate dose range capable of achieving a significantly altered state of consciousness (Passie, Halpern, Stichtenoth, Emrich, & Hintzen, 2008). Given these doses, an amount of LSD the size of an aspirin tablet would affect 3,000 people!

The high potency of LSD requires a different method for drug preparation. A common preparation method involves applying drops of a solution of LSD onto small squares of blotter paper or the glue sides of postage stamps. In either case, LSD sticks to the paper, and recreational users ingest the drug by licking the paper.

Through the oral administration route, LSD reaches peak absorption after 60 minutes. Cells in the liver metabolize LSD, producing *2-oxo-3-hydroxy-LSD*. LSD's elimination half-life is approximately three hours, which facilitates pharmacological effects lasting as long as eight hours (Passie et al., 2008).

## LSD and the Serotonin Neurotransmitter System

The chemical structure of LSD resembles serotonin's chemical structure, allowing LSD to act on serotonin receptors (**Figure 12.2**). Specifically, LSD functions as a receptor agonist with a high binding affinity for 5-$HT_{1A}$, 5-$HT_{2A}$, 5-$HT_{6}$, and 5-$HT_{7}$ receptors. In particular, LSD activates serotonin receptors located postsynaptically on other neurotransmitter neurons, such as glutamate and GABA neurons (Passie et al., 2008).

**Modal object completion** Perception of object boundaries inferred from incomplete representations of the object

These neurotransmission effects affect many sensory processing systems in the brain. In the visual cortex, LSD activates both 5-$HT_{1A}$ and 5-$HT_{2A}$ receptors, which can modify any number of visual processes (**Table 12.1**). For example, these actions can interfere with modal object completion for objects like those shown in **Figure 12.3**. **Modal object completion** is a perception of object boundaries inferred

**FIGURE 12.2** **Serotonin and LSD**

Portions of the LSD molecule resemble the chemical structure of the neurotransmitter serotonin.

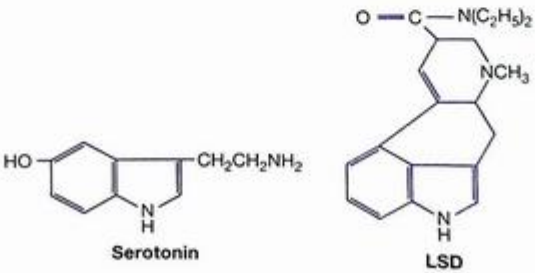
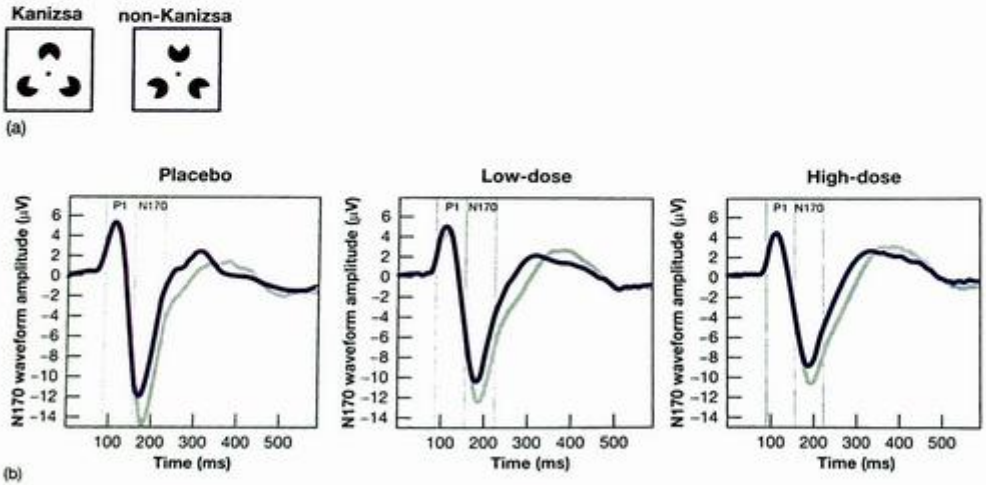


**TABLE 12.1 Effects of Hallucinogens on Structures in the Brain**

| Structure | Effects of Hallucinogen |
|---|---|
| Visual cortex | Alters visual processes, including modal object completion |
| Temporomedial cortex | Increases activity of this area, which is involved in complex visual processing |
| Cerebral cortex | Increases sensory signals to prefrontal cortex |
| Locus coeruleus | Decreases spontaneous activity, thereby sending normally suppressed sensory information to the cerebral cortex |
| Prefrontal cortex | Increases activity of the prefrontal cortex, the central sensory integration area of the cerebral cortex |

**FIGURE 12.3 LSD's Effects on Modal Object Completion**

A. LSD and other hallucinogens disrupt the ability to perceive nonexistent borders, a process called *modal object completion*, of Kanizsa objects, shown with a gray line (responses to non-Kanizsa objects shown by the purple line). B. During these tasks, hallucinogens impair the N170 waveform (the *N* stands for negative and the 170 refers to the location of the negative peak in milliseconds [ms]) in the occipital lobe on EEG recordings.




Source: Kometer et al. (2011). Reprinted with permission.

from incomplete representations of the object. According to electroencephalogram (EEG) recordings, the N170 waveform is strongly associated with modal object completion. In a study by Kometer et al. (2011) using human volunteers, the LSD-like hallucinogen psilocybin inhibited both modal object completion and weakened N170

waveform amplitudes in specific areas of the visual cortex. The objects viewed by participants consisted of *Kanizsa* objects, the perception of objects despite their lacking complete borders. Moreover, these reduced N170 waveform amplitudes correlated with overall decreased activity in the occipital lobe.

Hallucinogens also alter functioning in the locus coeruleus. In the locus coeruleus, LSD's activation of postsynaptic 5-$HT_{2A}$ receptors increases the activity of both glutamate and GABA neurons. Enhanced glutamate release increases sensory signals to the cerebral cortex. At the same time, GABA release decreases spontaneous activity in the locus coeruleus, causing greater refinement of sensory signals sent to the cerebral cortex. In essence, LSD causes normally suppressed sensory information from the locus coeruleus to become more refined and salient.

In the prefrontal cortex, the central integration area for processed sensory information, activation of 5-$HT_{2A}$ receptors by LSD also causes increased glutamate release. Enhanced glutamate release, in turn, increases activity in the prefrontal cortex. These findings correlate with human drug imaging data. In a positron emission tomography (PET) imaging study conducted by Vollenweider and colleagues (1997), the LSD-like hallucinogen psilocybin produced a significant increase in the metabolism of labeled glucose, an index of neuronal activity, in the prefrontal cortex. In addition, psilocybin elicited enhanced activity in the temporomedial cortex, a region involved in complex visual processing. These enhanced activity levels in the prefrontal cortex and temporomedial cortex also occurred while participants experienced visual hallucinations.

Chronic use of hallucinogens may cause structural changes to parts of the cerebral cortex. Bouso and colleagues (2015) found that long-term use of DMT correlated with a thinning of the posterior cingulate cortex. Further, those who self-reported more intense experiences of psychedelic effects from DMT were more likely to have thinner tissue in the posterior cingulate cortex. The researchers found this structure of particular interest because of its involvement in the brain's *default mode network*. The **default mode network** consists of activity occurring in a series of brain structures during times of non-goal-directed activity or inattention. When an individual disengages from a goal-directed task, we find the activity of brain structures switches to those parts of the default mode network.

**Default mode network**
Activity occurring in a series of brain structures during times of non-goal-directed activity or inattention

Psychologically, we find that the default mode network shifts thoughts away from goals in the moment toward self-referential thoughts. We do this in the absence of current demands, allowing us to think to ourselves. Thus, in this mode, we engage in thoughts about desires and beliefs, reflections on the past, and plans for our future (Buckner, Andrews-Hanna, & Schacter, 2008). Researchers have drawn analogy from Sigmund Freud's "ego" concepts to the default mode network, in that the ego allows for waking conscious thoughts about ourselves (Carhart-Harris & Friston, 2010).

**Ego dissolution** consists of a compromised sense of self during a psychedelic experience. Other terms used to describe ego dissolution include *ego death*, *ego loss*, and *ego disintegration*. Ego dissolution involves a blurring of the boundaries between one's sense of self and one's surroundings. In addition to psychedelic-induced ego dissolution, this phenomenon also occurs during intense mystical or spiritual experiences.

**Ego dissolution**
A compromised sense of self during a psychedelic experience

In order for researchers to more carefully characterize and rate ego dissolution from a psychedelic experience, Nour, Evans, Nutt, and Carhart-Harris (2016)

developed a self-report inventory that included a series of questions about ego dissolution—or the opposite, *ego inflation*—based on interviews with psychedelic users and experts in the field. Once developed and given to psychedelic users, statements endorsed regarding their psychedelic experience included experiencing a dissolution of "self," feeling at one with the universe, "a sense of union with others," decreased "sense of self-importance," less absorbed over own issues, "lost all sense of ego," and loss of "notion of self and identity." Also, regarding a psychedelic experience, they did not endorse ego inflation characteristics, such as feeling more important than others or feeling self-confident.

## STOP & CHECK

1. What is the most common administration route for LSD and other hallucinogens?
2. Although LSD activates many types of serotonin receptors, which receptor is most associated with visual hallucinations?
3. A hallucinogen may cause a temporary feeling of loss of self, which is referred to as _____.

1. oral administration 2. the 5-$HT_{2A}$ receptor 3. ego dissolution (or other names, such as ego death)

## LSD's Mild Physiological Effects and Profound Hallucinogenic Effects

LSD and many other serotonin-like hallucinogens primarily elicit subjective pharmacological effects. Even the LSD megadose taken by Hofmann—0.25 mg—produced few noticeable physiological effects. In his account of the trip, Hofmann said that his physician "found a rather weak pulse, but an otherwise normal circulation," and Hofmann felt fine the next day. At normally used doses, a person may exhibit only modest increases in heart rate, increases in pupil diameter, slight dizziness, mild nausea, diarrhea, or stomachache. The physiological safety of this drug is indicated by a human lethal dose of 14 mg, far above the doses capable of producing hallucinogenic effects (Brecher, 1972).

**True hallucination** Perception of images or sounds that are not real

**Pseudo-hallucinations** Altered perception of things that are real

**Trip** Hallucinogenic experience

**Good trip** Highly pleasant sensory distortions and pseudo-hallucinations

Although few, if any, physiological effects occur with normally used amounts, LSD and other serotonin-like hallucinogens exhibit pronounced subjective experiences. However, the term *hallucination* needs qualification. A **true hallucination** is a perception of images or sounds that are not real. Drugs such as LSD, on the other hand, normally produce **pseudo-hallucinations**, the altered perception of things that *are* real. Normal LSD doses cause distorted, waving, or kaleidoscopic forms of real images in a visual field (El-Mallakh & Walker, 2010). True hallucinations can occur with LSD, but they are considered rare (Passie et al., 2008).

As previously mentioned, the overall hallucinogenic experience is called a **trip**, and a trip can be good or bad. **Good trips** occur as highly pleasant sensory distortions and pseudo-hallucinations. During good trips, users may experience feelings of

enhanced perception or insightfulness. A user may also experience **synesthesia**, the experiencing of sensory stimuli in an incorrect sensory modality. LSD-elicited synesthesia, for example, often consists of experiencing sounds when seeing colors and vice versa (Brown, McKone, & Ward, 2010). The "From Actions to Effects" section later in this chapter describes synesthesia in greater detail. Hofmann, too, experienced synesthesia, stating that "sounds were transposed into visual sensations so that from each tone or noise a comparable colored picture was evoked, changing in form and color kaleidoscopically" (Brecher, 1972, p. 347).

**Synesthesia**
Experiencing sensory stimuli in an incorrect sensory modality

A **bad trip** is associated with disturbing true hallucinations, psychotic episodes, negative emotional states, altered perceptions of time, and out-of-body sensations (Eveloff, 1968). Hofmann experienced a bad trip after intentionally taking LSD. As noted earlier in this chapter, he stated that the faces of those around him "appeared as grotesque, colored masks" and that "I sometimes observed, in the manner of an independent neutral observer, that I shouted half insanely or babbled incoherent words." He reported that this experience was as if "I were out of my body" (Brecher, 1972, p. 347). Bad trips consist of the most commonly reported adverse effects from hallucinogen use.

**Bad trip**
Disturbing true hallucinations, psychotic episodes, negative emotional states, altered perceptions of time, and out-of-body sensations

A person's expectations and previous experiences affect LSD's subjective effects. Factors that affect a person's trip can include physical surroundings, current emotional state, comments made by friends, and many other factors. In fact, Eveloff (1968) states that profound skepticism about LSD's effects largely suppress the LSD experience. In general, users regard their mindset prior to LSD use and the impact of physical surroundings as "**set and setting**," referring to the influence these factors have on a psychedelic experience (Zinberg, 1984). LSD also causes **hypersuggestibility**, a state of easy influence by suggestions that can jeopardize reality testing. Eveloff (1968) reported that during some trips, users have jumped off buildings in the belief they could fly or stepped in front of traveling cars in the belief they lacked material substance.

**Set and setting**
Influence of mindset and physical surroundings on a psychedelic experience

**Hypersuggestibility**
A state of easy influence by suggestions that can jeopardize reality testing

The nature of hallucinogenic experiences presents an important challenge for hallucinogen research in animals. Even if an animal experienced something like a hallucinogenic trip, how could we tell? Rather than attempt to model such an experience, animal researchers instead study other features of hallucinogens such as their behavioral stimulus properties.

Winter and colleagues (2007) conducted a drug discrimination study using the hallucinogen psilocybin as the training drug in rats. After training rats in a task, the researchers conducted tests to determine the similarity between psilocybin's stimulus effects and those of other hallucinogenic drugs. As shown in **Figure 12.4**, rats exhibited stimulus generalization from mescaline to the hallucinogens LSD, psilocin, and DMT, demonstrating similar subjective effects between psilocybin and these compounds. Also recall that psilocin serves as the active metabolite for psilocybin.

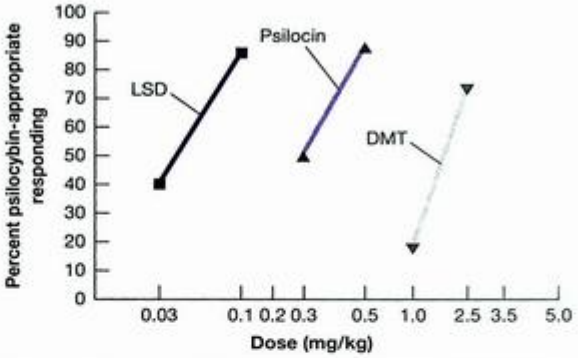
## Hallucinogens and Flashbacks

Occasionally, users may randomly experience a striking memory of the previous trip. Such an experience is referred to as a flashback or as a symptom of hallucinogen persisting perception disorder. These terms are used somewhat synonymously, but there are key differences in how the terms are applied. **Flashback** usually refers to a short, non-distressing recurrence of a previous trip. On the other hand,

**Flashback**
Random, short, and non-distressing memory of a previous hallucinogenic experience

**FIGURE 12.1 Many Hallucinogens Have Similar Stimulus Properties**

In a mescaline drug discrimination study, stimulus generalization occurred from mescaline to the hallucinogenic drugs LSD, psilocin, and DMT. Said another way, these drugs served as substitutes for the training drug psilocybin, causing rats to respond as if they were treated with psilocybin. The *y*-axis shows the percentage of responses occurring on the psilocybin lever, and the *x*-axis shows the doses of each drug tested.




Source: Adapted from Winter et al. (2007).

**Hallucinogen persisting perception disorder**
Recurring, lengthy, and unpleasant memory from a previous hallucinogenic experience

**hallucinogen persisting perception disorder** is characterized by recurring, longer-term, and unpleasant experiences that are difficult to reverse (Lerner et al., 2002). For example, a case study on hallucinogen persisting perception disorder described a patient who reported seeing afterimages. These included motions occurring in her peripheral field, halo effects flickering from objects that had a pattern on them, misperceiving the size of objects, and random spots of bright light (Hermle, Simon, Ruchsow, & Geppert, 2012).

In their review of hallucinogen persisting perception disorder cases and studies, Halpern and Pope (2003) noted difficulties in understanding the extent of prevalence and accuracy of diagnoses for this disorder. Flashbacks in particular, they found, seldom were defined the same across studies. Overall, they concluded that hallucinogen persisting perception disorder is an uncommon occurrence.

## STOP & CHECK

1. How does a true hallucination differ from a pseudo-hallucination?
2. How does a good trip differ from a bad trip?

1. A true hallucination is a perception of something not really there, whereas a pseudo-hallucination is an altered perception of something that really is there. 2. A good trip elicits a pleasurable psychedelic drug experience, whereas a bad trip elicits a distressful and disturbing experience.

## Mixed Stimulant–Psychedelic Drugs

Beyond the hallucinogens, other psychedelic drugs exhibit broader pharmacological effects. In particular, a **mixed stimulant–psychedelic drug** refers to a substance that exhibits both psychostimulant effects and hallucinations. One such drug is 3,4-methylenedioxymethamphetamine, better known by its common abbreviation **MDMA** or street name *Ecstasy*. A related compound to MDMA is 3,4-methylenedioxyamphetamine, referred to as MDA. MDA generally shares the same pharmacological actions and effects as MDMA and also is referred to as *Ecstasy*.

**Mixed stimulant–psychedelic drug**
Substance that exhibits both psychostimulant effects and hallucinations.

**MDMA**
A mixed stimulant-psychedelic drug.

*Ecstasy*, however, does not always refer to MDMA (or MDA). Instead, *Ecstasy* can refer to any number of stimulant or psychedelic preparations that may contain only small amounts, or even no amount, of MDMA. In an analysis of *Ecstasy* tablets collected by England's Forensic Science Service, a number of tablets contained another MDMA-like drug MDEA (3,4-methylenedioxyethamphetamine) instead of MDMA (Cole, Bailey, Sumnall, Wagstaff, & King, 2002). Other studies report *Ecstasy* pills containing methamphetamine, dextromethorphan, ketamine, and cocaine.

### Drug Profile: MDMA (3,4-methylenedioxymethamphetamine)

| | |
|---|---|
| Street name | *Ecstasy* (although the term does not always refer to MDMA) |
| Subjective effects | Produces stimulant effects and hallucinations, and enhances feelings of empathy and closeness with others |

Although MDMA is best known for its psychedelic and psychostimulant effects, it is also known as an **entactogen**, meaning "touching within," or as an **empathogen**, referring to "enhanced empathy." These terms synonymously refer to effects observed in early MDMA studies that users become friendlier, exhibit a closeness with others, and perceive greater insight into their thoughts and emotions (Nichols & Oberlender, 1990). Like LSD, these features made MDMA an attractive adjunctive medication for use in psychoanalysis (Rochester & Kirchner, 1999).

**Entactogen**
"Touching within," usually in reference to mixed stimulant-psychedelic drugs.

**Empathogen**
"Enhanced empathy," usually in reference to mixed stimulant-psychedelic drugs.

MDMA shares a similar chemical structure with amphetamine and possesses many of amphetamine's psychostimulant effects. Yet, MDMA also produces LSD-like hallucinations, so it fits into the mixed psychedelic–stimulant class of drugs. This class also includes the drugs AMT and 5-MeO-DIPT (Abraham et al., 2002). MDMA is frequently used in **raves**, large organized parties held in dance clubs or warehouses where electronic dance music is played with accompanying light

**Rave**
Large organized party held in a dance club or warehouse where electronic dance music is played with a light show.

displays. MDMA and other psychedelic drugs enhance this club experience (Miller & Schwartz, 1997).

MDMA users mainly consist of high school and college-age individuals. According to the National Institute on Drug Abuse, approximately four percent of 12th graders had used MDMA, and lifetime use of MDMA among those 25 years and younger was 10 percent (National Institute of Drug Abuse, 2020).

## MDMA Recreational Use

MDMA was developed in 1914 by Merck (the same company that had patented and distributed cocaine) during research efforts to develop amphetamine derivatives. Although studied for a time by the U.S. Army, the drug was popularized by experimental psychopharmacologist Alexander Shulgin for recreational use in the 1970s (McDowell & Kleber, 1994).

Shulgin's career walked a unique path between traditional laboratory scientist and club drug enthusiast. Shulgin was a chemist who had been educated at Harvard and Berkeley and had extensive training in pharmacology. He developed industrial chemicals for Bio-Rad Laboratories and Dow Chemical Company. At Dow, Shulgin developed *Zectran*, the first biodegradable pesticide. Shulgin also had a private laboratory at home, where he developed various psychedelic drugs, which he sampled himself and provided to his friends (Gems, 1999).

Shulgin played an important role in developing and promoting MDMA. After being introduced to the drug, Shulgin developed an easier synthesis method and reported the method to other psychedelic drug enthusiasts, allowing them to make it themselves. In 1976, Shulgin described MDMA's effects to Leo Zeff, a psychoanalyst who had used LSD on patients in the 1960s. Intrigued by Shulgin's account, Leo Zeff administered MDMA to several patients. Believing many of MDMA's subjective effects beneficial as a psychoanalytical agent, Zeff reported these accounts to colleagues, spurring an interest in MDMA for psychoanalysis that lasted until the 1980s (Pentney, 2001).

Beginning in the late 1970s, MDMA emerged as a recreational drug. People sought it for spiritual enlightenment, improving sensuality in relationships, and pure enjoyment. In humans, MDMA-related medical problems were purportedly rare, with only eight MDMA-related emergency room visits between 1977 and 1981. In laboratory animals, however, the occurrence of both acute and chronic adverse effects led to MDMA being labeled a dangerous drug. In 1985, despite opposition by therapists and recreational MDMA users, the DEA temporarily listed MDMA as a schedule I controlled substance, indicating high abuse potential and no therapeutic usefulness (Pentney, 2001; Rochester & Kirchner, 1999). The schedule I status was made permanent in 1988. The first clinical trial for MDMA in psychotherapy was published in 2011. The study, conducted by Mithoefer and colleagues (2011), reported that MDMA assisted therapy for patients with posttraumatic stress disorder (PTSD). In recent years, MDMA has been extensively pursued for the treatment of PTSD, and these findings are presented in Chapter 13.

## STOP & CHECK

1. Why is MDMA called an empathogen?
2. Although MDMA was developed decades earlier, who popularized MDMA in the 1970s?

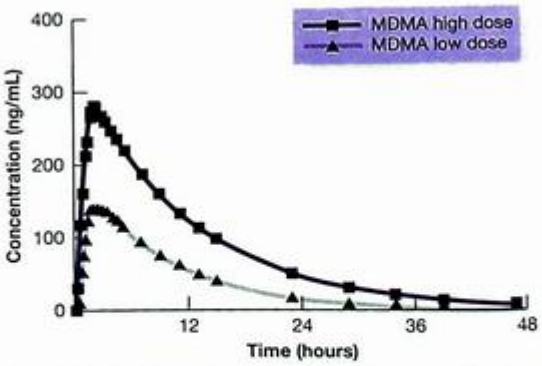
1. Empathogen is derived from the tendency of MDMA to induce friendliness, closeness with others, and greater insight into one's thoughts and emotions. 2. Psychopharmacologist Alexander Shulgin

## MDMA Metabolism and the Length of Psychedelic Drug Effects

MDMA users prefer to administer MDMA orally, usually through swallowing an MDMA-containing tablet. After swallowing a tablet, MDMA readily absorbs through the gastrointestinal tract, reaching peak blood plasma levels after approximately two hours. MDMA's elimination half-life is approximately nine hours (De La Torre, Farré, Roset, et al., 2000) (see **Figure 12.5**).

**FIGURE 12.5** **Elimination of MDMA**

MDMA (*Ecstasy*) remains in the body well beyond 24 hours, as shown for both a low dose (1.0 mg/kg) and high dose (1.6 mg/kg). The *y*-axis refers to the amount of MDMA in the blood, and the *x*-axis refers to time since MDMA administration.




*Source:* Kolbrich, E. A., Goodwin, R. S., Gorelick, D. A., Hayes, R. J., Stein, E. A., & Huestis, M. A. (2008). Physiological and subjective responses to controlled oral 3,4-methylenedioxymethamphetamine administration. *J Clin Psychopharmacol, 28*(4), 432–440. https://doi.org/10.1097/FTD.0b013e3181684fa0, p. 9. Reprinted with permission.

MDMA is metabolized in the liver primarily by CYP2D6 enzymes and to a lesser extent by other enzymes such as CYP1A2. CYP1A2 converts MDMA to methylenedioxyamphetamine (MDA), which produces similar effects, as noted earlier. Deficiencies in the CYP2D6 enzyme lead to accumulation of MDMA in the body. Approximately 10 percent of Caucasians exhibit these deficiencies. Accumulated MDMA leads to prolonged drug effects and an increased probability of adverse effects occurring at low to moderate doses. For example, certain *selective serotonin reuptake inhibitors* (SSRIs) such as *fluoxetine (Prozac)* inhibit CYP2D6 activity. These actions inhibit MDMA metabolism, leading to effects similar to those with inherent CYP2D6 deficiencies (Yang et al., 2006).

Inhibition of MDMA metabolism also can occur in people with fully functional CYP2D6 enzymes. De la Torre et al. (2000) studied the blood plasma levels of MDMA to determine MDMA's degradation rate. During this study, the researchers found that MDMA's elimination rate was not constant. Rather, MDMA metabolism slowed down over time. Based on these findings, taking further MDMA doses contributes to stronger and longer-lasting pharmacological effects than may otherwise be expected.

## MDMA and Serotonin and Dopamine Neurotransmission

Acute administration of MDMA alters serotonin neurotransmission at axon terminals through two mechanisms (**Figure 12.6**). First, MDMA inhibits serotonin transportation into synaptic storage vesicles. In doing so, MDMA prevents serotonin storage. Second, MDMA causes the reversal of serotonin membrane transporters. By reversing serotonin membrane transporters, MDMA expels any unstored serotonin (that wasn't catabolized by MAO) out into the synaptic cleft. Through these two mechanisms, MDMA produces an increase in extracellular brain serotonin levels. These increased serotonin levels lead in turn to increased activation of serotonin receptors (Rudnick & Wall, 1992).

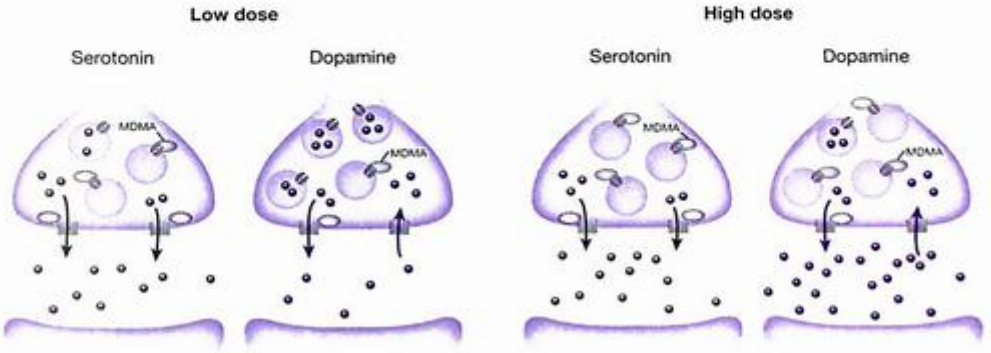
Like amphetamine, MDMA produces similar actions at dopamine axon terminals, leading to enhanced extracellular levels of dopamine in the brain (Figure 12.6). However, MDMA's effects on dopamine axonal terminals are weaker than its effects on serotonin axonal terminals. As a result, higher MDMA doses are necessary to enhance dopamine levels (Abraham et al., 2002; Steele, Nichols, & Yim, 1987).

Chronic administration of MDMA can produce severe damage to serotonin neurons. This damage appears according to every standard measure of serotonin neurons, including loss of brain serotonin, the serotonin metabolite 5-hydroxyindolacetic acid (5-HIAA), tryptophan hydroxylase, and the serotonin membrane transporter. Hatzidimitriou and colleagues (1999) provided a striking example of MDMA-induced neuronal loss in monkeys.

In this study, researchers treated monkeys with MDMA daily over four days. Two weeks after treatment ended, MDMA-treated monkeys had a dramatic decline in serotonin neuron axons, as shown in the middle panels of **Figure 12.7**. Serotonin

**FIGURE 12.6 MDMA's Effects on Serotonin and Dopamine Axon Terminals**

MDMA produces dose-dependent effects on serotonin and dopamine neurotransmission. At lower doses (left), MDMA effectively inhibits serotonin entry into vesicles and reverses the serotonin reuptake transporter direction. These actions cause large enhancements in serotonin release. Few effects occur at dopamine axon terminals at low doses, producing minimal changes in dopamine release. At higher doses (right), MDMA remains effective at enhancing serotonin levels. Yet, we also find inhibited entry of dopamine into vesicles and a reversal of the dopamine membrane transporter direction. This combination of actions causes significant enhancements of dopamine levels as well.

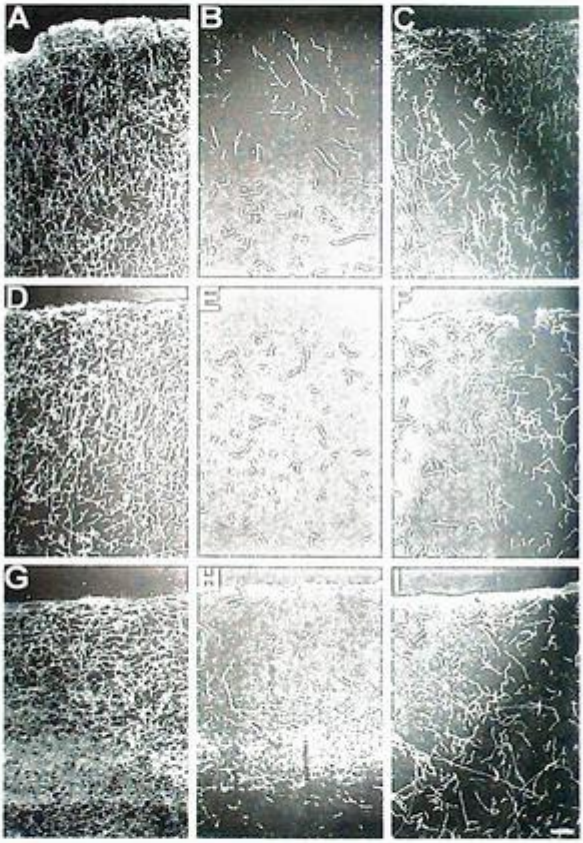



neuron loss remained low in a monkey assessed seven years after this experiment, as shown in the right panel of Figure 12.7. This finding suggests a severe neurotoxic effect from repeated MDMA use and a dismal likelihood of neuronal recovery.

Because the cellular techniques used in animals cannot be used in living humans, we lack precise indices of MDMA-induced neurotoxic function in humans. However, the limited data available, in concert with extensive animal data, suggest that serotonin neuron loss occurs in human MDMA users as well. First, heavy MDMA users have lower 5-HIAA levels in cerebrospinal fluid, suggesting less serotonin production in their nervous systems (McCann, Ridenour, Shaham, & Ricaurte, 1994). Second, PET imaging techniques reveal lower levels of serotonin membrane transporters in routine MDMA users. For example, Erritzoe and colleagues (2011) found reduced serotonin membrane transporter levels in routine MDMA users. Particularly striking, frequent hallucinogen use, such as LSD or mescaline, did not have reductions in serotonin membrane transporter levels in users. However, MDMA-induced reduction in serotonin membrane transporter levels may not be permanent. Selvaraj and colleagues (2009) failed to find serotonin membrane transporter reductions in heavy MDMA users who had refrained from MDMA use for more than one year.

**FIGURE 12.7 MDMA Toxicity for Serotonin Neurons**

Four days of MDMA administration led to a significant reduction in cortical serotonin neurons two weeks after treatment (middle panels) and seven years after treatment (right panels) compared to a monkey treated with placebo (left panels). The top row of panels (A, B, and C) were dark-field photomicrograph sagittal sections from the frontal cortex. The middle panels (D, E, and F) were taken from the parietal cortex, and the bottom panels (G, H, and I) were taken from the primary visual cortex.




*Source:* Hatzidimitriou et al. (1999).

## STOP & CHECK

1. How might a drug that inhibits CYP2D6 activity, such as fluoxetine, affect the pharmacokinetics of MDMA?
2. What are the key differences in pharmacological actions between low and high MDMA doses?
3. What effect does heavy MDMA use have on serotonin neurons?

1. The CYP2D6 enzyme metabolizes MDMA. Any drug that inhibits CYP2D6 activity will slow down MDMA metabolism, causing prolonged MDMA effects. 2. Lower MDMA doses primarily enhance serotonin neurotransmission, whereas higher MDMA doses enhance both serotonin and dopamine neurotransmission. 3. Heavy, sustained MDMA use destroys serotonin neurons.

### MDMA's Psychedelic and Psychostimulant Effects

The effects that MDMA has in a party setting may differ from those reported under carefully controlled laboratory conditions. These differences occur for multiple reasons. First, as stated earlier in this chapter, the term *Ecstasy* inconsistently refers to MDMA. A so-called *Ecstasy* tablet may include MDMA, but it also may contain other drugs (Cole et al., 2002). Second, MDMA is seldom taken alone. For example, many club goers take MDMA while consuming alcohol (Mohamed, Hamida, Pereira de Vasconcelos, Cassel, & Jones, 2009). Third, an individual may take MDMA while also taking prescribed psychoactive medications. For example, an individual taking certain antidepressant drugs may have an exaggerated reaction to MDMA's effects (Mohamed, Hamida, Cassel, de Vasconcelos, & Jones, 2011). Fourth, MDMA's effects vary depending on the dose administered (Abraham et al., 2002).

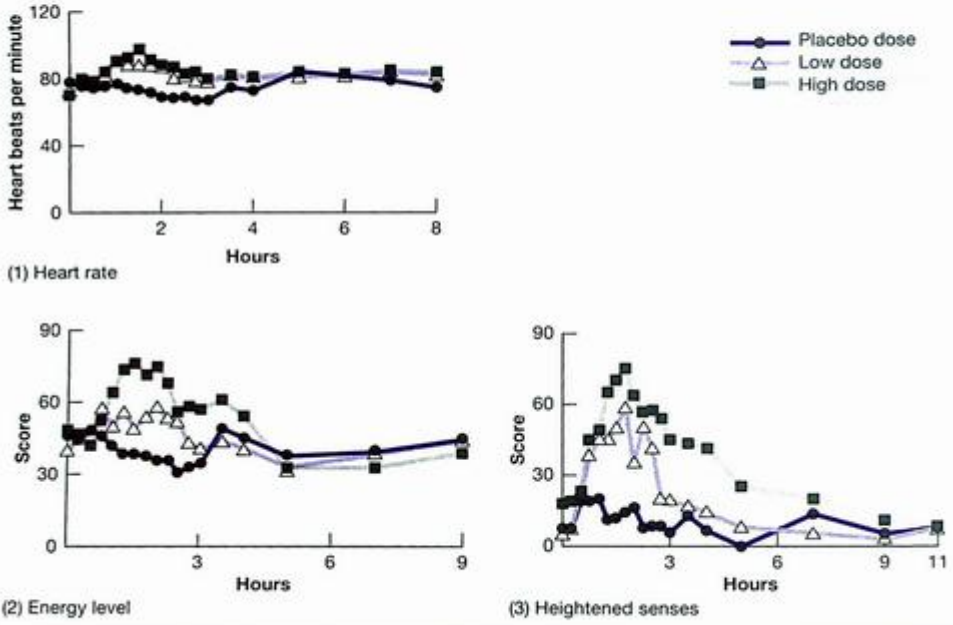
MDMA's physiological effects resemble those of psychostimulant drugs such as amphetamine at higher doses. For example, Kolbrich and colleagues (2008) assessed the effects of low (1.0 mg/kg) and high (1.6 mg/kg) doses of MDMA in occasional MDMA users (**Figure 12.8**). In these volunteers, only the high MDMA dose produced an increase in heart rate and blood pressure.

**Review!** Psychostimulant drugs activate the sympathetic nervous system (Chapter 6).

Low MDMA doses elicit few physiological effects. However, both low and high MDMA doses elicit significant subjective effects. In the same study, Kolbrich and colleagues (2008) found that low MDMA doses produced feelings or sensations of

**FIGURE 12.8** **MDMA's Effects on Heart Rate, Sense of Energy, and Heightened Awareness**

In human volunteers, a high MDMA dose increases sympathetic nervous system effects such as (1) heart rate and (2) a sense of energy. Both low and high doses create (3) perceptions of heightened senses. Scales were used to assess degree of energy level and heightened senses.




*Source:* Kolbrich, E. A., Goodwin, R. S., Gorelick, D. A., Hayes, R. J., Stein, E. A., & Huestis, M. A. (2008). Physiological and subjective responses to controlled oral 3,4-methylenedioxymethamphetamine administration. *J Clin Psychopharmacol, 28*(4), 432–440. https://doi.org/10.1097/FTD.0b013e3181684fa0, p. 9. Reprinted with permission.

heightened senses, racing thoughts, and euphoric effects. The high MDMA dose included these effects as well as perceptions of increased energy and feelings of closeness to others (Figure 12.8).

The subjective effects of MDMA relate to both psychostimulants and hallucinogenic drugs. Tancer and Johanson (2003) recruited human volunteers to assess the effects of MDMA compared to the psychostimulant d-amphetamine and the hallucinogen metachlorophenylpiperazine (mCPP). *mCPP* binds to all serotonin receptors and acts as an agonist; in addition, mCPP inhibits serotonin reuptake through serotonin transporters (Baumann, Ayestas, Dersch, & Rothman, 2001; Hamik & Peroutka, 1989). mCPP has mostly been used as a study compound by researchers, but we now find mCPP used recreationally as another psychedelic drug with purported hallucinogen-like effects (Bossong et al., 2010). Like d-amphetamine, MDMA

produced increases in a scale for drug "liking," an indication of reinforcing effects. Similar to mCPP, MDMA produced increases in perception and hallucinogen-like effects. There were also shared traits among these drugs. MDMA, d-amphetamine, and mCPP increased ratings of friendliness and talkativeness. Each drug also increased a sense of improved cognition (Tancer & Johanson, 2003).

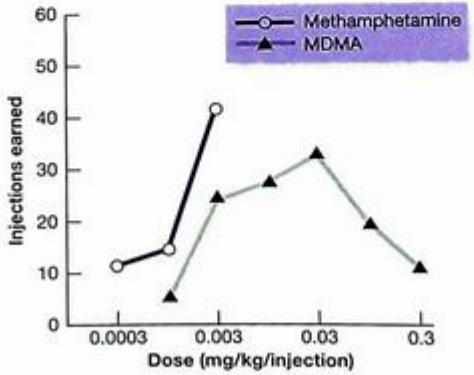
## Drug Profile: metachlorophenylpiperazine (mCPP)

| | |
|---|---|
| Street name | Also described as *Ecstasy* |
| Uses and effects | Primarily used as a research compound; some reports of recreational use as a hallucinogen |

Based on animal models, MDMA exhibits reinforcing effects, although in comparison, conventional reinforcing drugs such as methamphetamine produce stronger reinforcing effects. For example, Fantegrossi and colleagues (2002) examined the reinforcing effects of MDMA and methamphetamine in monkeys using a self-administration model. Across a range of doses, subjects self-administered significantly less MDMA compared to methamphetamine (**Figure 12.9**).

**FIGURE 12.9 Self-Administration of Methamphetamine and MDMA**

Rhesus monkeys self-administered methamphetamine more readily compared to MDMA. The *y*-axis shows the number of drug injections the monkeys earned during a session, and the *x*-axis shows the number of doses of self-administered drugs.




*Source:* Adapted from Fantegrossi, W. E., Ullrich, T., Rice, K. C., Woods, J. H., & Winger, G. (2002). 3,4-Methylenedioxymethamphetamine (MDMA, "ecstasy") and its stereoisomers as reinforcers in rhesus monkeys: serotonergic involvement. *Psychopharmacology (Berl), 161*(4), 356–363, p. 9.

Beyond reinforcing effects, MDMA is also the representative drug for empathogens, which, as stated earlier, refer to enhanced empathy. Women appear more sensitive to MDMA's psychedelic and empathogenic properties than men. In fact, Leicht and colleagues (2001) found that women exhibited a greater sensitivity to nearly every measure of MDMA's effects, including overall improved mood, feelings of depersonalization, time perception changes, and emotional sensitivity. Moreover, women experienced more frequent and profound visual perception changes such as visual hallucinations (pseudo), synesthesia, and memories.

As stated previously, animals poorly model psychedelic effects uniquely experienced by humans. However, animal models *can* provide indexes of sociability. Morley and McGregor (2000) used a social interaction test to compare relatively low MDMA doses to placebo. After administration, MDMA-treated rats exhibited fewer aggressive behaviors and greater social interactions with other rats compared to placebo-treated rats (**Box 12.1**).

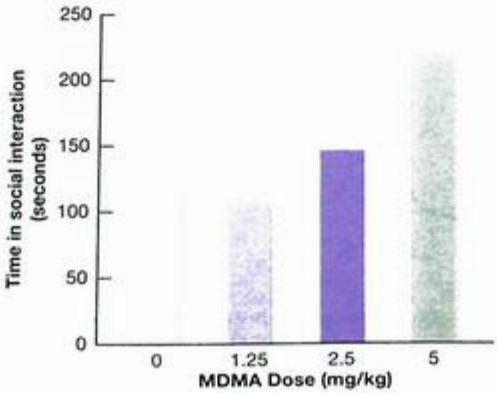
# BOX 12.1

## SOCIAL INTERACTION TESTS

Social interaction tests assess the effects that drugs have on animal social behavior. These assessments use naturally social species, such as rats, and involve observing any of several key social behaviors after placing animals together. Social behaviors in rats, for example, include sniffing, following, and crawling over or under each other.

**BOX 12.1 FIGURE 1** **Effects of MDMA in a Rodent Social Interaction Test**

In a social interaction test, rats treated with the 5.0 mg/kg dose of MDMA spent significantly more time interacting with other rats compared to saline-treated rats. The *y*-axis shows time spent interacting with other rats, and the *x*-axis refers to the dose of MDMA. The zero (0) dose refers to saline.



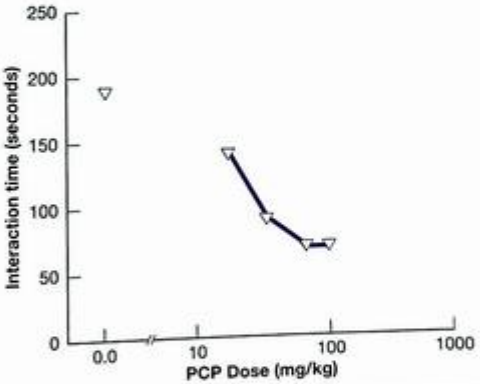

Source: Morley and McGregor (2000). Reprinted with permission.

In a typical social interaction test in rats, a researcher places two or more rats together in an open field. After placing rats in the box, researchers score the number of social behaviors, including sniffing, nudging another rat with their snouts, and closely following other rats. To ensure accurate behavioral recording, multiple researchers may score a social interaction test session and compare their scores afterward.

Psychedelic drugs affect rodent behavior in social interaction tests. For example, Morley and McGregor (2000) tested the stimulant–psychedelic drug using this test. This study found that MD spent significantly more time interacting compared to saline-treated rats (**Box** Using a different psychedelic drug, Sar evaluated the effects of the dissoci phencyclidine (PCP) on social behavio conducting a social interaction test, P exhibited reduced social interactions saline-treated rats (**Box 12.1 Figure 2**). PCP-treated rats appeared socially with

**BOX 12.1 FIGURE 2** **Effects of PCP in a Rodent Social Interaction Test**

Phencyclidine-treated rats exhibited significantly reduced social interactions compared to vehicle-treate interaction test. The *y*-axis refers to time spent interacting with other rats, and the *x*-axis shows the PCP (0) dose refers to vehicle.




*Source:* Adapted with permission from Macmillan Publishers Ltd: Nature, Sams-Dodd, F. (1998). Effects of continuou phencyclidine administration on social behaviour, stereotyped behaviour, and locomotor activity in rats. *Neuropsych* 18–25. doi:S0893133X97002005 [pii]. Copyright © 1998.

## MDMA's Adverse Effects

Like the pharmacological effects already described, elevated dopamine and serotonin levels account for MDMA's adverse effects. Like the hallucinogens, MDMA also can lead to flashbacks and hallucinogen persisting perception disorder likely due to its actions on serotonin neurotransmission (Litjens, Brunt, Alderliefste, & Westerink, 2014). MDMA shares adverse effects with many psychostimulant drugs such as methamphetamine. Physiologically, higher doses of MDMA, which are

achieved by taking two or more standard MDMA doses, such as 1.6 mg/kg, can substantially activate the sympathetic nervous system, leading to significant increases in heart rate, breathing rate, blood pressure, and body temperature (De La Torre, Farré, Roset, et al., 2000; Kolbrich et al., 2008). This is one of the most common causes of unconsciousness from MDMA use. Other serious problems include brain hemorrhaging and chaotic heartbeat (Kolbrich et al., 2008).

In raves, where dancing occurs in crowded conditions, MDMA use can lead to severe overheating and dehydration, increasing the risk of multiple organ failure. **Multiple organ failure** from MDMA use is a serious medical event that, in addition to hyperthermia and dehydration, is associated with seizures, muscle breakdown, kidney failure, and blood vessel blockade. Liver damage may also occur because of contaminants produced during MDMA synthesis (Abraham et al., 2002; McDowell & Kleber, 1994).

**Multiple organ failure**
Occurs due to hyperthermia from MDMA use, resulting in seizures, muscle breakdown, kidney failure, and blood vessel blockade

Psychologically, MDMA doses may cause adverse effects, including paranoia, true hallucinations, panic, and delirium. Moreover, MDMA overdose can cause impulsive irrational behavior such as walking into the middle of street traffic or attempting to jump from buildings several stories high (Hooft & van de Voorde, 1994; Kaye, Darke, & Duflou, 2009; McDowell & Kleber, 1994).

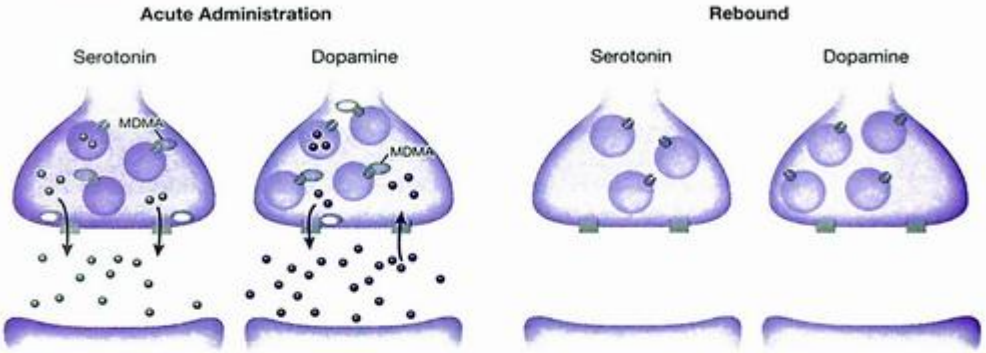
Rebound effects occur from normal MDMA use. Rebound normally occurs after 24 hours from MDMA use and primarily consists of depression and lethargy. These effects are related to MDMA's pharmacological actions at dopamine and serotonin axon terminals. As described previously, MDMA empties stored serotonin and dopamine from axon terminals and prevents serotonin and dopamine reuptake. These actions leave serotonin and dopamine stores temporarily depleted. Replenishing these stores requires synthesizing new serotonin and dopamine molecules, a process that can take several days for full recovery (**Figure 12.10**) (Parrott, 2001).

Cognitive deficits occur from repeated MDMA use. These deficits particularly affect verbal working memory. During verbal working memory tasks, where a participant recalls words given minutes earlier, former heavy MDMA users perform poorer compared to non-recreational drug users or non-MDMA polydrug users (Schilt et al., 2010). In particular, MDMA users do more poorly on complex verbal memory tasks.

For example, Brown and colleagues (2010) studied verbal working memory in long-term MDMA users and compared their results to those of long-term cannabis users and non-recreational drug users. The researchers conducted several tasks ranging from simple tasks, in which an individual freely recalled words from a list, to complex tasks, in which an individual recalled words grouped within triplets of associated words. In the associated word triplets, the investigator might have read out loud *frog–chair–apple*, later prompting the participant with the word *frog* and requesting the remaining two words. The results? MDMA users performed well on the simple free-word recall task, but not on the difficult triplet-word association task. Given these results, MDMA users appear to have sustained deficits in complex verbal working memory that may fail to improve over time.

**FIGURE 12.10 MDMA's Rebound Effects and Neurotransmission**

Acute administration of sufficiently high MDMA doses (left) produces an increase in serotonin and dopamine release. A rebound effect occurs after the stores of dopamine and serotonin have emptied (right), resulting in diminished serotonin and dopamine levels.




## STOP & CHECK

1. How do low-dose MDMA subjective effects differ from high-dose MDMA subjective effects?
2. Why might taking MDMA and dancing at a party be a bad idea?
3. Why do rebound effects occur after MDMA use?

1. Low MDMA doses produce feelings or sensations of heightened senses, racing thoughts, and reinforcing effects. High MDMA doses include these effects—and perceptions of increased energy levels and feelings of closeness to others. 2. MDMA enhances sympathetic nervous system activity, making an individual prone to hyperthermia, increased heart rate, and hyperventilation. Engaging in physically exerting activities in this state can lead to unconsciousness, brain hemorrhaging, and chaotic heartbeat. 3. Rebound effects are the result of emptied serotonin and dopamine synaptic pools. The diminished neurotransmitter levels account for depression and lethargy.

## MDMA Tolerance and Withdrawal

Shulgin, the psychopharmacologist who promoted MDMA, reported that MDMA's positive effects declined after the first seven uses, anecdotally describing tolerance

to MDMA's effects. Novice users soon increase the number of MDMA tablets consumed in order to continue achieving positive subjective effects. Experienced MDMA users may take as many as 10–20 tablets in a single occasion. However, a potential confound in this reporting is that, according to MDMA users, MDMA tablets are steadily getting weaker (Parrott, 2001).

A characterization of withdrawal symptoms depends on whether or not to consider *rebound* as a sign of dependence. Rebound fails to meet the classical view on withdrawal symptoms, which normally develop after long-term use. Rebound, instead, could occur after first-time use. When excluding rebound from consideration as withdrawal, researchers seldom find withdrawal symptoms, including any indications of physical dependence or psychological dependence such as drug craving (Parrott, 2001).

Despite a lack of withdrawal by the typical definition, Cottler and colleagues (2001) found that close to half of MDMA users surveyed met the DSM criteria for a substance use disorder. Sixty-three percent of those surveyed indicated using MDMA despite having knowledge of its harmful effects. Furthermore, 43 percent reported MDMA use in reckless situations, such as driving a vehicle or having unprotected sex. Thirty-nine percent spent a lot of time trying to obtain and use MDMA.

## STOP & CHECK

1. Although somewhat controversial, what are the main arguments that MDMA is an addictive substance?

1. First, MDMA exhibits tolerance to subjective effects. Second, many recreational users continue taking MDMA despite knowing the drug is harmful.

**Dissociative anesthetics**

**Phencyclidine**

**Ketamine**

## Dissociative Anesthetics

**Dissociative anesthetics** are sedative pain-relieving drugs that produce feelings of disconnectedness from the body along with depressant and stimulant effects. Not all of these effects occur at the same time but instead depend on the dose taken. There are three primary dissociative anesthetics. **Phencyclidine**, also known by the street names *PCP* or *angel dust*, is the most abused dissociative anesthetic. **Ketamine**, also known as *Special K* or *K*, is another recreationally used dissociative anesthetic. Beyond these drugs, dozens of chemical analogues of phencyclidine exhibit similar pharmacological effects (Abraham et al., 2002; Soine, 1986). In recent years, ketamine has come to be known as an experimental antidepressant drug, as covered in Chapter 13.

## Drug Profile: phencyclidine

| | |
|---|---|
| Street name | *PCP, angel dust* |
| Uses | Recreational purposes; most abused among dissociative anesthetics |

## Drug Profile: ketamine

| | |
|---|---|
| Street name | *Special K, K* |
| Uses | Recreational purposes; used with animals as an anesthetic |

Like most psychedelic drugs, phencyclidine and other dissociative anesthetic use occurs in party or club settings. Phencyclidine comes in a variety of forms, including pills, powder, and liquid (Pradhan, 1984). Clandestine laboratories provide the main source of phencyclidine and other dissociative anesthetic drugs (Soine, 1986). The U.S. Drug Enforcement Administration lists phencyclidine and ketamine as schedule II substances, reflecting the DEA's view that dissociative anesthetics not only have high abuse potential but also legitimate medical uses (Drug Enforcement Administration, 2012b). This scheduling also allows for clinical investigations on other uses for dissociative anesthetics, such as evaluating ketamine as an antidepressant drug (see Chapter 13).

### Development of Phencyclidine, Ketamine, and Dizocilpine

Like most psychedelic drugs, phencyclidine, ketamine, and dizocilpine were first developed by pharmaceutical companies. *Phencyclidine*, the first dissociative anesthetic drug, was discovered in 1926 by Parke, Davis, and Company during a development program for anesthetic drugs. Phencyclidine was used as a veterinary anesthetic and later used as an anesthetic in humans. In humans, however, patients reported experiencing nightmares, severe anxiety, delusional thoughts, and delirium after recovering from anesthesia. *Ketamine* was also used as an anesthetic drug in humans but was soon discontinued for adolescents and adults because of similar disturbing effects. Yet, we do not find these effects occurring in children, and therefore, ketamine may still be used for this population. Ketamine also remains a common veterinary anesthetic (Abraham et al., 2002; Domino & Luby, 2012).

After abandoning dissociative anesthetics for human anesthetic uses, dissociative anesthetic use continued in two different directions. The first was recreational

use. Phencyclidine emerged as a recreational drug during the 1960s. Regarded for relaxing effects, phencyclidine was referred to as the *PeaCe Pill*, leading to the popular street name *PCP*. Users refer to its powder form as *angel dust*. Phencyclidine received a bad street reputation in San Francisco during the mid-1960s because of the disturbing effects similar to those experienced by phencyclidine anesthesia patients. However, phencyclidine use reappeared in the 1970s and remains a popular recreational substance (Lerner & Burns, 1978).

The second direction for dissociative anesthetic use was psychiatric research. As discussed later in this section, human phencyclidine or ketamine use produces a temporary psychological state remarkably similar to schizophrenia. Phencyclidine-like dissociative anesthetics exhibit hallucinations, paranoia, and other positive schizophrenia symptoms, as well as emotional affect, social withdrawal, and other negative schizophrenia symptoms. Phencyclidine and related dissociative anesthetics also elicit schizophrenia-like cognitive impairments. These pharmacological characteristics led to a new neurological model for understanding schizophrenia, which is described in greater detail in Chapter 15 (Jentsch & Roth, 1999).

## Absorption and Elimination of Phencyclidine

Phencyclidine administration includes intravenous injection, inhalation, and insufflation. Phencyclidine was used orally during the 1960s, but users since then have shifted to using the powder form. With the powder form, users insufflate, intravenously inject, or smoke phencyclidine. Further, users may administer phencyclidine with other drugs, such as sprinkling phencyclidine powder onto cannabis joints (Lerner & Burns, 1978).

The administration route affects the onset time for drug effects. Smoking phencyclidine leads to psychoactive effects within one to five minutes and reaches peak effects within five to 30 minutes after administration. Insufflation achieves drug effects within 30 seconds to one minute (Lerner & Burns, 1978). After absorption, phencyclidine's elimination half-life is 18 hours, but it can be as long as 51 hours (Cook, Perez-Reyes, Jeffcoat, & Brine, 1983). Thus, a single administration of phencyclidine produces long-lasting effects.

## STOP & CHECK

1. What is the key psychedelic effect of dissociative anesthetics?
2. How long does phencyclidine remain in the body?

1. Dissociative anesthetic drugs produce feelings of disconnectedness from the body. 2. Phencyclidine, the representative drug for dissociative anesthetics, has an elimination half-life of 18 hours, which accounts for long-lasting pharmacological effects.

## Phencyclidine's Effects on Dopamine and Serotonin Neurotransmission

Phencyclidine, as well as ketamine and dizocilpine, exhibit a number of pharmacological actions in the nervous system. Overall, phencyclidine affects serotonin,

**TABLE 12.2 Effects of Phencyclidine on Neurotransmission**

| Neurotransmitter | Effects |
|---|---|
| Serotonin | Enhances serotonin levels by inhibiting reuptake and functioning as an agonist for 5-$HT_{2A}$ receptors |
| Dopamine | Enhances dopamine levels by inhibiting reuptake and functioning as a partial agonist for $D_2$ receptors |
| Acetylcholine | Acts as a non-competitive antagonist for nicotinic receptors at neuromuscular junctions and autonomic nervous system ganglia; also an antagonist for muscarinic receptors |
| Endogenous opioids | Activates opioid kappa receptors |
| Glutamate | Antagonist for glutamate NMDA receptors; interferes with long-term potentiation |

dopamine, acetylcholine, and glutamate neurotransmission (**Table 12.2**) (Abraham et al., 2002; Jentsch & Roth, 1999). Phencyclidine causes enhanced serotonin neurotransmission through at least two key mechanisms (see **Figure 12.11**). First, phencyclidine causes inhibition of the serotonin membrane transporter. This action prevents serotonin reuptake and causes serotonin levels outside the neuron to increase. Greater serotonin levels cause an increase in serotonin receptor activation. Second, phencyclidine functions as an agonist at 5-$HT_{2A}$ receptors (Kapur & Seeman, 2002; Smith, Meltzer, Arora, & Davis, 1977).

Phencyclidine has similar actions on the dopamine system (see Figure 12.11). On dopamine axon terminals, we also find inhibition of reuptake through dopamine membrane transporters. As with serotonin, this action causes an increase in dopamine levels outside of the neuron, which facilitates activation of dopamine receptors. Phencyclidine is also a partial agonist for dopamine $D_2$ receptors (Kapur & Seeman, 2002; Smith et al., 1977).

**Review!** A partial agonist is a drug that binds to a receptor but has a weaker ability, compared to full agonists, for activating the receptor (Chapter 4).

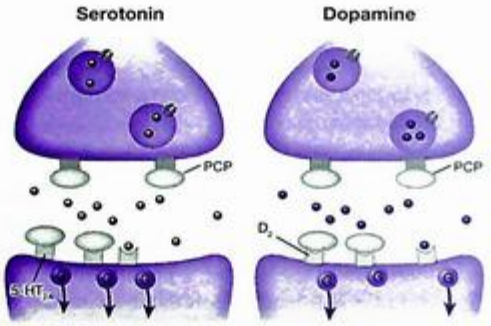
Phencyclidine also acts on other neurotransmitter systems. At higher concentrations, phencyclidine functions as a non-competitive antagonist for cholinergic nicotinic receptors at neuromuscular junctions and at ganglia in the peripheral nervous system. Phencyclidine's actions at neuromuscular junctions cause muscles to contract. At ganglion cells, phencyclidine alters sympathetic and parasympathetic nervous system activity (Fryer & Lukas, 1999). High concentrations of phencyclidine-like drugs also antagonize cholinergic muscarinic receptors in the central and autonomic nervous systems. Higher concentrations also activate opioid kappa receptors (Hustveit, Maurset, & Oye, 1995).

## Dissociative Anesthetics and Glutamate Neurotransmission

In addition to the actions already described, phencyclidine and similar dissociative anesthetics function as antagonists for glutamate NMDA (N-methyl-D-aspartate)

**FIGURE 12.11 Effects of Phencyclidine and Serotonin and Dopamine Neurotransmission**

Phencyclidine enhances serotonin neurotransmission (left) by inhibiting serotonin reuptake transporters and activating 5-$HT_{2A}$ receptors. Activating 5-$HT_{2A}$ receptors stimulates associated G proteins. Phencyclidine enhances dopamine neurotransmission (right) through inhibiting dopamine membrane transporters and by functioning as a partial agonist for dopamine $D_2$ receptors. As a partial agonist, phencyclidine activates some $D_2$ receptors while failing to activate others. PCP = phencyclidine, G = G protein.




receptors. As described in Chapter 4, NMDA receptors are ionotropic and contain binding sites for many substances on the ion channel's subunits. The NMDA receptor's channel contains a binding site for phencyclidine and the other dissociative anesthetics covered in the section. When binding to this site, phencyclidine prevents positively charged ions from entering the channel. By preventing NMDA receptor activation, phencyclidine interferes with a process called long-term potentiation (Abraham et al., 2002).

**Long-term potentiation**
Form of synaptic plasticity important for learning and memory

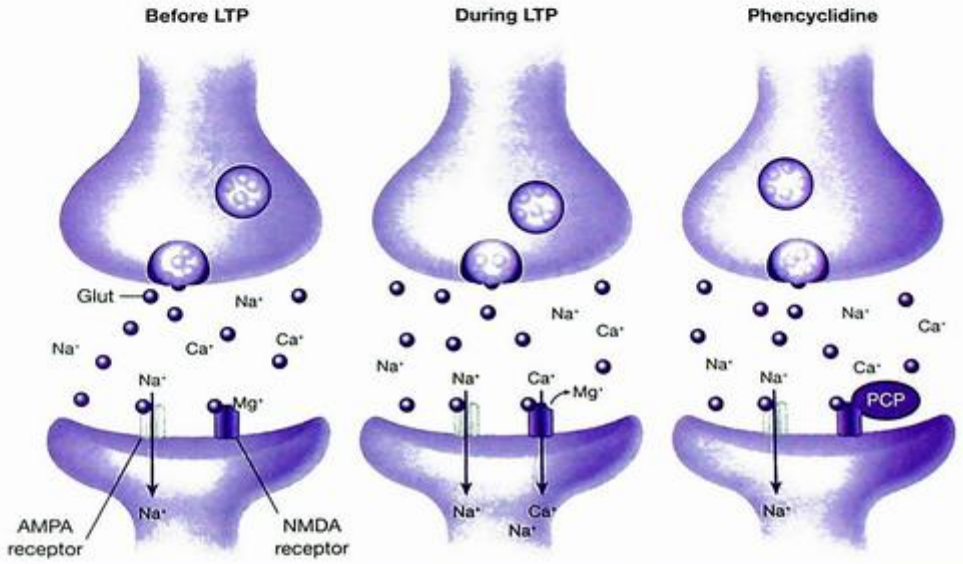
**Long-term potentiation** is a form of synaptic plasticity critical for learning and memory. *Potentiation* means "strengthening," and *plasticity* refers to adaptive change in neural characteristics, often occurring at synapses. Long-term potentiation depends on postsynaptic glutamate AMPA and NMDA glutamate receptors and the neurotransmitter glutamate (**Figure 12.12**).

At these synapses, glutamate binds to both AMPA and NMDA receptors. Before long-term potentiation, however, glutamate only successfully activates AMPA receptors. Activation fails to occur at NMDA receptors because a $Mg^{+2}$ ion blocks the NMDA receptor channel, preventing ions from entering the channel. Long-term potentiation occurs when the membrane depolarizes sufficiently to repel the $Mg^{+2}$ ion from the channel. Sufficient membrane depolarization occurs as a result of repeated and sustained AMPA receptor activation.

**Review!** Both glutamate AMPA and NMDA receptors produce excitatory postsynaptic potentials by allowing the entry of positively charged ions such as $Na^+$ (Chapter 3).

**FIGURE 12.12 Long-Term Potentiation**

Before long-term potentiation (left synapse), a magnesium ion prevents other ions from entering the NMDA receptor channel. During long-term potentiation (middle synapse), sustained activation of the AMPA receptors elicits sufficient depolarization to expel the magnesium ion from the NMDA receptor channel. The expulsion of magnesium supports a stronger synaptic connection by enabling positively charged ions to the neuron through the NMDA receptor channel. Phencyclidine and other dissociative anesthetic drugs block the NMDA receptor channel. By blocking the NMDA receptor channel, phencyclidine disables long-term potentiation. LTP = long-term potentiation, Glut = glutamate, $Na^+$ = sodium, $Ca^+$ = calcium, $Mg^+$ = magnesium, PCP = phencyclidine.




Once depolarization changes dislodge the $Mg^{+2}$ ion from the NMDA channel, $Na^+$ and $Ca^{2+}$ ions can pass through the NMDA receptor channel. The entry of additional positively charged ions leads to greater membrane depolarization and facilitates neuronal excitability. Thus, by dislodging the $Mg^{+2}$ ion from the NMDA channel, glutamate becomes more effective in exciting the neuron—that is, by creating excitatory postsynaptic potentials. When phencyclidine enters the brain, it acts at NMDA receptors by blocking the receptor's channel. In doing so, phencyclidine prevents long-term potentiation from forming or disrupts currently existing long-term potentiated synapses.

**Review!** *Excitatory postsynaptic potentials* refers to excitatory input from other neurons that result in membrane depolarization (Chapter 3).

## STOP & CHECK

1. What effects do dissociative anesthetic drugs have on serotonin and dopamine neurotransmission?
2. AMPA and NMDA glutamate receptors are critical for _____, a form of synaptic plasticity critical for learning and memory.
3. How does a dissociative anesthetic drug such as phencyclidine interfere with long-term potentiation?

1. Dissociative anesthetics prevent serotonin and dopamine reuptake. They also function as agonists for 5-HT$_1$ receptors and as partial agonists for dopamine D$_2$ receptors. 2. long-term potentiation 3. Phencyclidine binds to a site with the NMDA channel, which prevents ions from entering the neuron through the NMDA channel. This action weakens the postsynaptic neuron's response to the presynaptic neuron.

### The Anesthetic and Psychedelic Effects of Dissociative Anesthetics

Phencyclidine's behavioral effects change by dose. At lower doses, phencyclidine elicits a drunken-like state. These doses exhibit CNS depressant effects. Moreover, users often report a numbness in fingers and toes, an indication of anesthetic effects. At moderate doses, these drugs produce appreciable numbness throughout the body. These doses relate to an enhanced CNS depressant effect.

Phencyclidine offers unique psychedelic effects compared to LSD and MDMA. In particular, phencyclidine elicits a feeling of disconnectedness from the body. In particular, recreational dissociative anesthetic users also report **out-of-body experiences**, the sensation of floating above one's body or even viewing one's body as if one is separate from it. This property led to classifying phencyclidine and related drugs as *dissociative* anesthetics.

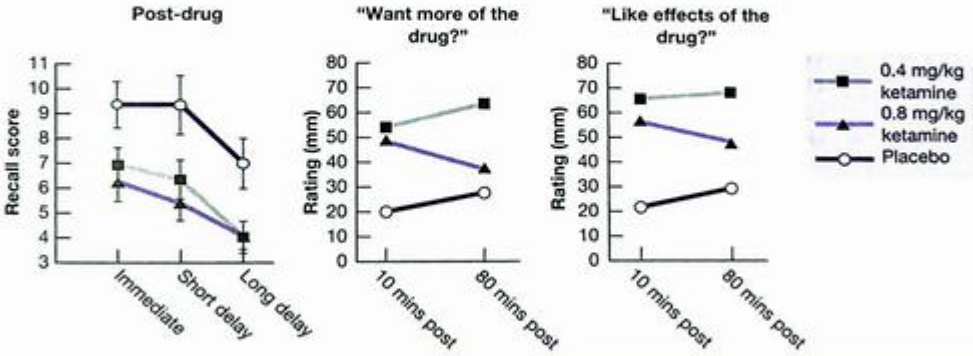
**Out-of-body experience**
The sensation of floating above one's body or even viewing one's body as if one is separate from it.

Moderate doses also impair memory. Thus, dissociative anesthetic users may have a rich psychedelic experience yet cannot remember it later. These memory-impairing effects likely relate to disruption of long-term potentiation. By acting like $Mg^{+2}$ ions that block NMDA receptors, dissociative anesthetics prevent long-term potentiation and, ultimately, the formation of memories (Abraham et al., 2002). Results from numerous studies suggest that frequent use of ketamine, and likely other dissociative anesthetics, leads to deficits in short- and long-term memory (Morgan & Curran, 2012).

In a study conducted by Morgan and colleagues (2004), human volunteers were assessed on a series of pharmacological measures during intravenous infusion of the phencyclidine-like drug ketamine. When asked to recite a message they heard played from a recorder either 10 or 80 minutes earlier, ketamine-treated patients recalled significantly fewer words compared to placebo-treated patients (**Figure 12.13**).

**FIGURE 12.13 Assessment of Ketamine's Memory and Rewarding Effects**

In a study by Morgan and colleagues (2004), both low and high ketamine doses in humans led to significantly poorer recall of a message played either 10 minutes earlier (short delay) or 80 minutes earlier (long delay) (left figure). Ketamine also elicited agreement with the question "Want more of the drug?" (middle) and "Like effects of the drug?" (right).




Source: With kind permission from Springer Science+Business Media: Morgan, C. A., Mofeez, A., Brandner, B., Bromley, L., & Curran, H. V. (2004). Ketamine impairs response inhibition and is positively reinforcing in healthy volunteers: a dose–response study. *Psychopharmacology, 172*(3), 298–308. doi:10.1007/s00213-003-165, p. 10.

Whereas low and moderate doses elicit depressant effects, high phencyclidine doses produce psychostimulant effects. These include an amphetamine-like rush and other increased arousals. Peripherally, high phencyclidine doses elicit sympathetic nervous system activation, leading to increased heart rate, blood pressure, respiration rate, body temperature, and other sympathetic nervous system effects (Siegel, 1978).

Further, phencyclidine psychostimulant effects account for differences in self-administration studies compared to hallucinogens such as LSD. Unlike LSD, animals learn to self-administer phencyclidine. This phencyclidine property was first discovered in 1973 by Robert Balster and colleagues (1973). In this study, rhesus monkeys initiated lever responding in order to receive intravenous injections of phencyclidine. Data such as these strongly suggest that phencyclidine produces reinforcing effects in humans as well.

Morgan and colleagues (2004) also found evidence of reinforcing effects with dissociative anesthetics in humans. During ketamine infusion, participants gave positive responses to reinforcer-related questions posed by the researchers, including "Want more of the drug?" and "Like effects of the drug?" Placebo-treated participants reported none of these positive responses (Figure 12.13).

## Dissociative Anesthetics and Schizophrenia-Like Effects

Many of phencyclidine's severe adverse effects occur at large doses. At these doses, phencyclidine can produce cataleptic-like effects on movements. The effect

is associated with antagonism of nicotinic cholinergic receptors at neuromuscular junctions.

As first described in the history of dissociative anesthetics, a schizophrenia-like state is another adverse effect. This episode of schizophrenia persists for days and even weeks. In the study conducted by Morgan and colleagues (2004) described previously, the phencyclidine-like drug ketamine produced effects that measured as schizophrenia-like symptoms on a psychiatric scale. The production of schizophrenia-like states led to the *glutamate hypothesis of schizophrenia*. The glutamate hypothesis basically states that schizophrenia symptoms manifest from diminished glutamate neurotransmission. Chapter 15 provides more information about this hypothesis for schizophrenia.

### Tolerance and Withdrawal Effects With Dissociative Anesthetics

Generally, phencyclidine or ketamine users administer these drugs once a week or less. The separation of drug administrations by days or weeks prevents the development of tolerance. However, for those who take phencyclidine or ketamine on a regular basis, greater doses become necessary to achieve similar pharmacological effects, a clear indication of tolerance.

For the same dosing reasons already described, dependence on phencyclidine, ketamine, or other dissociative anesthetics seldom occurs. When it does, it manifests as psychological withdrawal symptoms. These symptoms include craving the drug or feeling lethargic and depressed. These drugs rarely produce physical dependence (Lerner & Burns, 1978).

## STOP & CHECK

1. At which doses do the anesthetic effects of a dissociative anesthetic drug occur?
2. Which effects of dissociative anesthetic drugs relate to interference of long-term potentiation?
3. How do the reinforcing effects of dissociative anesthetics compare to the hallucinogen LSD?

1. Numbness occurs at low doses and becomes more pronounced at moderate doses. 2. memory disruptive effects 3. Unlike LSD, animals learn to self-administer dissociative anesthetics. In addition, humans report enjoying the dissociative anesthetic drug ketamine. Overall, dissociative anesthetics appear to exhibit greater reinforcing effects than LSD.

## Other Psychedelic Drugs

As is apparent from the drugs covered so far in this chapter, we find an ever-growing list of psychedelic drugs, including newly synthesized drugs, discovered constituents in plants, and reassessed effects of already known substances. To this end, a

coverage of all psychedelic drugs is beyond the scope of this text. However, three other types of these drugs need mentioning.

The first is **dextromethorphan**, an opioid receptor drug and cough suppressant found in many over-the-counter cold medications. Because of its presence in *Robitussin* cough syrups, recreational dextromethorphan users, who mainly consist of adolescents, refer to consuming large amounts of cough syrup to achieve psychedelic effects as *Robo-tripping*. At cough suppressant doses, dextromethorphan functions primarily as an opioid receptor agonist, just like the prescription opioid cough suppressant codeine. Higher doses lead to an appreciable production of dextromethorphan's active metabolite dextrorphan, a glutamate NMDA receptor antagonist. Other opioids that exhibit NMDA antagonism include methadone and ketobemidone (Ebert, Andersen, & Krogsgaard-Larsen, 1995). Together, these actions produce pharmacological effects similar to both opioid receptor agonists, like morphine, and NMDA receptor antagonists, like phencyclidine.

**Dextromethorphan**
Opioid receptor drug used in cough suppressant that in large-enough doses can produce psychedelic effects.

## Drug Profile: dextromethorphan

| | |
|---|---|
| Brand name | Sold as *Robitussin* cough syrup (and generic brand names); recreational use referred to as Robo-tripping |
| Actions | Agonist for opioid receptors and antagonist for NMDA receptors |
| Effects | Suppressing cough; psychedelic effects consist of visual perceptual changes, feelings of transcendence, and mystical experiences |

Users can achieve enjoyable and stimulating drug effects after ingesting 100 mg of dextromethorphan, roughly equivalent to 25 ml of over-the-counter cough syrup. Psychedelic effects, similar to those produced by dissociative anesthetics, occur at doses near 475 mg, equivalent to about 120 ml, or one full 4-ounce bottle of cough syrup. Psychedelic effects consist of visual perceptual changes, feelings of transcendence, and mystical experiences (Reissig et al., 2012). In direct comparison between dextromethorphan and psilocybin in human participants, the subjective effects of both drugs were mostly similar (Carbonaro, Johnson, Hurwitz, & Griffiths, 2018).

The second drug is **Salvinorin A**, the psychoactive constituent in *Salvia divinorum*. *Salvia divinorum* is referred to as *magic mint* and *diviner's sage*. Recreational users administer Salvinorin A by chewing or smoking *Salvia* leaves. Unlike LSD, Salvinorin A exhibits no activity at 5-$HT_{2A}$ receptors (Roth et al., 2002). It differs from LSD by also functioning as an agonist for kappa opioid receptors. The discovery of this pharmacological action suggests that kappa opioid receptors play a role in sensory perception (Chavkin et al., 2004; Roth et al., 2002). Salvinorin A also produces modest increases in dopamine levels in the nucleus accumbens in rats

**Salvinorin A**
Psychoactive compound found in *Salvia divinorum*, referred to as *magic mint* or *diviner's sage*.

(Braida et al., 2008). Salvinorin A users report experiencing visions and perceptions, such as becoming objects, revisiting places from the past, depersonalization, uncontrollable laughter, and perceptions of being several places at once from amounts as low as 0.2–1.0 mg (Siebert, 1994).

## Drug Profile: Salvinorin A

| | |
|---|---|
| Street name | *Magic mint, diviner's sage* |
| Actions | Agonist for kappa opioid receptors |
| Effects | Visions; perceptions of becoming objects, revisiting places from the past; depersonalization; uncontrollable laughter |

Animal research findings suggest that Salvinorin A also produces reinforcing effects. Salvinorin A administration produces a conditioned place preference in zebrafish and rats (Braida et al., 2008; Braida et al., 2007). Rats self-administer lower doses of intravenously administered Salvinorin A (Braida et al., 2008).

Muscarinic receptor antagonists such as *scopolamine* and *atropine* represent another type of psychedelic drug. Both scopolamine and atropine occur naturally in plants such as *Atropa belladonna*, which is known as deadly night shade, and *Datura stramonium*, which is also known as Jamestown weed. These substances have ancient histories of human use, including medicinal and religious practices (Schultes, 1969). Scopolamine and atropine produce true visual hallucinations, delusional thinking, and disorientation about time and place by acting as antagonists for muscarinic cholinergic receptors in the central and peripheral nervous systems (Goudie et al., 2001; Watanabe et al., 1978). Scopolamine or atropine use also causes dry mouth, hypertension, and urinary retention, owing to blockade of cholinergic receptors in the parasympathetic nervous system (Shervette, Schydlower, Fearnow, & Lampe, 1979).

**Muscimol**
Psychedelic compound in *Amanita muscaria*

The mushroom *Amanita muscaria* (also known as *fly agaric* or *fly amanita*) is another type of psychedelic mushroom that exhibits psychedelic effects. The mushroom's key psychoactive compound **muscimol** produces hallucinogenic effects through activation of $GABA_A$ receptors. In particular, muscimol features a high affinity for $\delta$-$GABA_A$ receptors, which do not bind with benzodiazepines, are especially sensitive to the neurotransmitter GABA, and reside outside of synapses (Benkherouf et al., 2019). *Amanita muscaria* mushrooms are found through Europe and Russia, and shamanistic use of these mushrooms was common in Siberia, in northern Russia. The mushrooms also served as a source of vitamin D for this region of the world, which sees short daytimes in winter. Thus, Siberians might have consumed these mushrooms for different reasons, and could therefore have had psychedelic experiences. Some historians have looked at the associations of potential *Amanita muscaria* use and its potential influence on traditional stories from the

region, such as flying reindeer (Bouchard, 2017). Moreover, Lewis Carroll's *Alice in Wonderland* is frequently cited for connotations of psychedelic experiences, including mushrooms—for example, a caterpillar tells Alice that the mushroom it's sitting on is the key to a strange journey, making her grow or shrink in size with different bites (Jay, 2003).

## Drug Profile: scopolamine

| | |
|---|---|
| Actions | Antagonist for cholinergic muscarinic receptors |
| Effects | True visual hallucinations, delusional thinking, and disorientation about time and place |

## Drug Profile: atropine

| | |
|---|---|
| Actions | Antagonist for cholinergic muscarinic receptors |
| Effects | True visual hallucinations, delusional thinking, and disorientation about time and place |

## STOP & CHECK

1. What is the psychedelic compound found in over-the-counter cough syrups such as *Robitussin DM*?
2. Although Salvinorin A elicits hallucinogenic effects through activating 5-$HT_{2A}$ receptors, what other pharmacological action might contribute to the compound's psychedelic effects?
3. Why are scopolamine and atropine unattractive recreational psychedelic substances?

1. dextromethorphan 2. Salvinorin A also functions as an agonist for kappa opioid receptors. 3. Scopolamine, atropine, and other muscarinic receptor antagonists exhibit confusion and delusional thinking. In particular, these drugs exhibit profound inhibition of memory.

## From Actions to Effects: Synesthesia

As noted earlier in this chapter, some psychedelic drug users experience a phenomenon called *synesthesia*. Although occurring during some hallucinogenic experiences,

synesthesia commonly arises without an apparent cause. In fact, about one in 23 individuals routinely experiences synesthesia in normal, everyday situations—we refer to these individuals as *synesthetes*. Synesthetes report these experiences as normal and generally pleasant (Hubbard, 2007). Further, studies indicate no reliable association between psychiatric conditions and synesthesia. Beyond synesthetes, many experience a synesthesia-like effect in the form of sounds, such as "silent flashers" when viewing bright, sharp images, or so-called "noisy gifs." According to one study, musicians were more likely to experience sounds when viewing noisy gifs. The term used is "visual-evoked auditory response," referred to by the acronym *vEAR* (Fassnidge et al., 2019).

Several neurobiological models exist to explain synesthesia. One model implicates potential abnormalities in portions of the brain where multiple sensory modalities meet. For example, the *temporo-parietal-occipital junction*, the meeting point for the parietal, occipital, and temporal lobes, may lack proper inhibitory feedback functioning during synesthesia. Improper feedback may, in turn, lead to additional sensory perceptions to a single sensory stimulus. Other models suggest that synesthesia reflects an abnormality in processes that integrate sensory information into a single multisensory scene (Hubbard, 2007).

**Review!** Visual processing first takes place in the occipital lobe. The parietal lobe assesses touch information and contributes to visual processing. The temporal lobe processes auditory information as well as visual processing (Chapter 2).

Although the neurobiology of innately occurring synesthesia remains uncertain, drug-induced synesthesia presents a clearer picture. Perception researchers Brang and Ramachandran (2008) described several lines of evidence linking 5-$HT_{2A}$ receptor activation to hallucinogen-induced synesthesia. The first line of evidence is that 5-$HT_{2A}$ receptor agonists such as LSD produce synesthesia. Second, antidepressant drugs acting as serotonin reuptake inhibitors inhibit synesthesia. The elevated serotonin levels caused by serotonin reuptake inhibitors lead to the activation of 5-$HT_{1A}$ receptors that, in turn, *reduce* 5-$HT_{2A}$ activation, a mechanism that counteracts synesthesia. Chapter 14 provides more information about the interactions between 5-$HT_{1A}$ and 5-$HT_{2A}$ receptors.

Third, antidepressant drugs acting as norepinephrine reuptake inhibitors also inhibit synesthesia. Similar to the second mechanism described already, elevated norepinephrine levels lead to greater activation of $\alpha_2$ adrenoceptors, which also reduce 5-$HT_{2A}$ receptor activation. Fourth, melatonin causes synesthesia in some individuals. Melatonin inhibits serotonin levels, reducing the inhibitory influence 5-$HT_{1A}$ receptors have on 5-$HT_{2A}$ receptors. By removing the inhibitor, 5-$HT_{2A}$ receptor-induced synesthesia becomes more likely to occur. Based on these four reasons, Brang and Ramachandran (2008) suggest that 5-$HT_{2A}$ receptors are, in fact, *synesthesia receptors*.

## STOP & CHECK

1. Is synesthesia a mental disorder?
2. Which receptor likely accounts for hallucinogen-induced synesthesia?

1. Synesthesia is not considered a mental disorder: It correlates poorly with psychiatric disorders, and individuals do not find synesthetic experiences disturbing or disruptive. 2. the 5-$HT_{2A}$ receptor

## CHAPTER SUMMARY

Psychedelic drugs include a long list of substances that vary in effects, ranging from hallucinations, sensory distortion, delusions, and dissociation. The three primary psychedelic drug classes are hallucinogens, mixed stimulant–psychedelics, and dissociative anesthetics. The representative drug for hallucinogens, LSD, closely resembles the chemical structure of neurotransmitter serotonin and subsequently functions as an agonist for many serotonin receptors. Activation of 5-$HT_{2A}$ receptors in particular leads to visual hallucinations as well as synesthesia. In addition to hallucinations, LSD produces a suggestible state that can lead to altered perceptions of reality.

Mixed stimulant–psychedelic drugs exhibit effects similar to both psychostimulant drugs such as amphetamine and hallucinogenic drugs such as LSD. MDMA, the representative drug for mixed stimulant–psychedelic drugs, elevates sensory perceptions at lower doses by enhancing serotonin neurotransmission and produces additional psychostimulant effects at higher doses by enhancing dopamine neurotransmission.

Dissociative anesthetics such as phencyclidine and ketamine produce both depressant and psychostimulant effects along with anesthesia, feelings of disconnectedness from the body, and memory-impairing effects. These effects arise from enhancing serotonin and dopamine neurotransmission as well as from blocking glutamate NMDA receptors, which are important for memory function.

Many other psychedelic drugs exist. Dextromethorphan found in *Robitussin* cough syrup elicits morphine-like euphoria and dissociative anesthetic-like psychedelic effects. Salvinorin A, found in the plant *Salvia divinorum*, produces hallucinogenic effects by serving as an kappa opioid receptor agonist. Muscarinic receptor antagonists, such as scopolamine, produce hallucinations, delirium, confusion, delusions, and poor judgment. Muscimol is found in the mushroom *Amanita muscaria* and produces psychedelic effects through a subtype of $GABA_A$ receptors.

## KEY TERMS

Psychedelic drugs 377
Hallucinogens 378
Lysergic acid diethylamide (LSD) 378
Psilocybin 378
Dimethyltryptamine (DMT) 379
Quanah Parker 381
Albert Hofmann 381
Harvard Psilocybin Project 382
Modal object completion 383
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Salvinorin A 411
Muscimol 412

CHAPTER 13

# Treatments for Depression and Bipolar Disorder

## Chapter Outline

- Mental Disorders
- Depression
- Antidepressant Drugs
- Limitations in Antidepressant Drug Effectiveness and Development
- Pharmacogenetic Factors in Antidepressant Treatment
- Combination Drug Strategies for Treating Depression
- Combining Psychotherapy and Pharmacotherapy for Treating Depression
- Antidepressant Drugs and Monoamine Neurotransmitter Systems
- Bipolar Disorder
- Mood Stabilizers, Anticonvulsants, Antipsychotics, and Antidepressants for Bipolar Disorder
- From Actions to Effects: Psychedelic Drugs for Treating Depression

## Learning Objectives

- Describe the clinical and biological features of depression and bipolar disorder
- Associate the pharmacological actions of antidepressant drugs with types of antidepressants and their pharmacological effects
- Associate the pharmacological actions of drugs for bipolar disorder with their pharmacological effects

The preceding chapters of this text concerned changes in brain function and behavior caused by psychoactive substances. Thus, normal behavior became abnormal after a drug was administered. For mental illness, we instead find behavior abnormal before treatment, and the goal of psychoactive therapeutic drugs is to change behavior toward a less problematic state. The subsequent chapters of this text shift from drugs of abuse to those used for treating mental disorders, which we refer to as *psychotropic drugs*, *therapeutic drugs*, or *pharmacotherapeutic drugs*.

## Mental Disorders

**Mental disorder**
Impairment in normal behavioral, cognitive, or emotional functioning

Just as we have referred to the *Diagnostic and Statistical Manual* (DSM) for defining substance use disorders, we also refer to the DSM for defining different types of mental disorders. We consider a **mental disorder** as an impairment in normal behavioral, cognitive, or emotional functioning. Mental disorders are highly prevalent throughout the world and occur across all demographics. According to the World Health Organization (WHO), an estimated 450 million people qualify for a mental disorder diagnosis, whereas many others have various symptoms associated with mental disorders. Based on 2017 estimates, 264 million individuals have depression, and 800,000 commit suicide annually (GBD 2017 Disease and Injury Incidence and Prevalence Collaborators, 2018). Despite the tremendous impact that poor mental health has on a society, only one percent of health costs are devoted to mental health in low- to middle-income countries (World Health Organization, 2016).

To diagnose a mental disorder, the DSM generally requires that an individual experience significant dysfunction and stress and that the disorder does not arise from a medical condition with a clear physiological cause. For example, the DSM does not qualify Alzheimer's disease as a mental disorder, despite clear changes in mental functioning, because the disease derives from a clear organic cause. This distinction came from a time when neuroscience technology had not advanced sufficiently to glean physiological causes for mental disorders. We will learn much about the neurobiology of DSM mental disorders in these remaining chapters and focus on how therapeutic drugs alter biological processes to improve mental functioning. The subsequent chapters cover the following major mental disorders: depression, bipolar disorder, anxiety, and schizophrenia.

## Depression

**Major depressive disorder**
Disorder characterized by at least five depressive symptoms that last two weeks or longer

According to the DSM-5, **major depressive disorder** is characterized by at least five symptoms occurring over the course of a two-week period. These symptoms must at least include either depressed mood or a lack of interest or pleasure in activities once enjoyable. Including having one or both of these symptoms, a patient must have five symptoms from those listed in **Table 13.1**, including change in body weight, change in sleep patterns, fatigue, feelings of worthlessness, difficulties in thinking or concentrating, and thoughts of suicide. The DSM also labels major depressive disorder by severity—mild, moderate, and severe. All meet the criteria for major depressive disorder, but clinicians can rate a disorder above mild if more than the minimum symptoms occur or by the degree of impairment the symptoms cause (American Psychiatric Association, 2013a).

**TABLE 13.1 Symptoms of Depressive Disorders**

| Disorder | Symptoms May Include: |
|---|---|
| Major depressive disorder | Depressed mood occurring daily and for most of the day |
| | Anhedonia (lack of pleasure) and disinterest |
| | Changes in body weight (gain or loss) |
| | Changes in sleep patterns (insomnia or hypersomnia) |
| | Fatigue and loss of energy |
| | Agitation or slowing of movement |
| | Feelings of worthlessness and guilt |
| | Difficulty thinking and making decisions |
| | Recurrent thoughts of suicide |
| Persistent depressive disorder | Same as those for major depressive disorder |
| Specifiers | Additional symptoms to those for depression, depending on the specifier. For example, the specifier "with anxious distress" includes anxiety symptoms and the specifier "with psychotic features" includes hallucinations and delusions. |

Depression also may occur in a milder form called **persistent depressive disorder** (or **dysthymia**). The primary symptoms for persistent depressive disorder include a depressed mood that regularly exists for at least two years. In addition, individuals diagnosed with dysthymic disorder must have at least two symptoms listed for major depressive disorder.

**Persistent depressive disorder (or dysthymia)** A disorder that includes a depressed mood that occurs nearly every day for at least two years

Clinicians also recognize that other conditions may accompany depression, something that the DSM classifies as *specifiers*. A clinician, for example, might find significant features of anxiety accompanying a clear diagnosis of major depressive disorder. In this instance, the clinician would diagnose the patient with major depressive disorder, along with the specifier "with anxious distress." Adding this specifier may inform treatment directions. For example, the patient may receive medications for both depression and anxiety.

In addition to a specifier for anxiety, we also find that some depressed individuals exhibit delusions or hallucinations. In this context, a clinician would add the specifier "with psychotic features." When we find psychosis present in depression, hallucinations and delusions tend to relate to depressed mood and negative thoughts. For

example, an individual may have delusions that she has cancer all throughout her body or that no one wants her to live. An individual may hear voices stating the same types of things. Those with psychosis and depression may benefit from medications to treat both types of symptoms (Spiker et al., 1985). The DSM notes many other types and specifiers for depression, as well.

We also find a degree of cognitive dysfunction in depression. The degree and types of cognitive impairment tend to vary across studies, owing in large part to the age of participants, severity of depression, and other population differences. In general, individuals with severe depression tend to exhibit impairments in episodic memory, an ability to explicitly describe one's memory of certain past experiences (Goodwin, 1997; Zakzanis, Leach, & Kaplan, 1998). Further, those with major depressive disorder also exhibit reduced ability to sustain attention (Zakzanis et al., 1998). Cognitive function normalizes when depressive symptoms subside (Paelecke-Habermann, Pohl, & Leplow, 2005).

Another condition consists of postpartum depression, enduring feelings of depression, anxiety, and exhaustion following childbirth (Wisner, Parry, & Piontek, 2002). Postpartum depression occurs in approximately 12 percent of women (Shorey et al., 2018). A diagnosis of postpartum depression differs from what might be referred to as the *baby blues*, in that this condition describes tiredness, worry, and lack of happiness following childbirth that recede on their own after a few weeks.

Postpartum depression reaches a level of moderate to severe depression and likely derives from a combination of the difficulties with the situation of raising a young infant in addition to biological causes. In particular, women experience a sudden decline in estrogen and progesterone, which has been experimentally shown to induce a depressive state in women with a history of postpartum depression (Bloch et al., 2000). The active metabolite of progesterone, allopregnanolone, functions as a positive allosteric modulator of $GABA_A$ receptors—specifically $GABA_A$ receptors with an $\alpha_4$ subunit, which are located in the hippocampus and amygdala (Smith, Shen, Gong, & Zhou, 2007). A form of allopregnanolone for intravenous administration is marketed as brexanolone (*Zulresso*) and indicated for treating postpartum depression. When administered, the drug requires 60 continuous hours of administration. A drug with similar pharmacological action—zuranolone—is currently under investigation to be used as an oral medication (Zorumski, Paul, Covey, & Mennerick, 2019).

## STOP & CHECK

1. What is the major distinction between a neurological disorder and a mental disorder?
2. How is major depressive disorder different from persistent depressive disorder?
3. Which hormones have reduced levels following childbirth?

1. If the condition causing abnormal behavior has a clear organic cause. Then it is a neurological disorder. Otherwise, it is a mental disorder that can be diagnosed by the DSM. 2. Major depressive disorder requires more diagnosis symptoms than dysthymic disorder, and the symptoms for major depressive disorder need only last two weeks, whereas a depressed mood for dysthymic disorder must consistently occur for two years. 3. estrogen and progesterone

## The Prevalence of Depressive Disorders

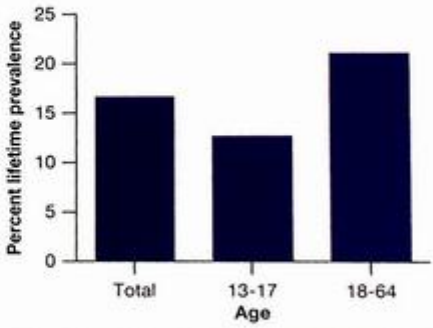
Depression is the fourth leading cause of disability worldwide due to its prevalence and impact on quality of life (Murray & Lopez, 1997). According to a U.S. national survey conducted by Kessler, Petukhova, Sampson, Zaslavsky, and Wittchen (2012), the prevalence of major depressive disorder during a lifetime is 16.6 percent (**Figure 13.1**). Yet, we find much higher rates among university students. In a review of published reports on depression among university students, Ibrahim and colleagues (2013) found that an average of approximately 30 percent of students met the DSM criteria for a depressive disorder.

Women are twice as likely to be diagnosed with major depressive disorder as men. Some of these differences in prevalence may derive from different depressive symptoms occurring in men than in women. Depressed men tend to exhibit greater irritability, over-reactivity, impulsivity, anger, aggression, and substance abuse as symptoms more often than women. On the other hand, women are more likely to exhibit heavy, leaden feelings in arms or legs (known as *lead paralysis*) and greater fatigue (Winkler, Pjrek, & Kasper, 2005). Differences such as these may result in women meeting the standard definitions of major depressive disorder more often than men. To determine whether this might be a factor, Martin, Neighbors, and Griffith (2013) examined rates of depression by comparing more conventional diagnostic criteria to criteria that included certain depressive symptoms more common in men. When factoring in aggression, substance abuse, and risk-taking behavior, the researchers found no gender differences in rates of depression.

Approximately one out of six individuals with major depressive disorder commits suicide, and the Centers for Disease Control and Prevention (CDC) estimates that

**FIGURE 13.1 Prevalence of Depression**

The lifetime likelihood of experiencing depression is approximately 16 percent (left). The likelihood is also shown for 13-17 years of age (middle) and for 18-64 years of age (right).




*Source:* Data from Kessler et al. (2012).

as many as 12 to 25 suicide attempts are made for every suicide death. Men are nearly twice as likely to commit suicide as women. Suicide is the third-highest cause of death in teenagers, but it is far more likely to occur in male adolescents and young adults than in female adolescents and young adults. One-third of those who commit suicide test positive for alcohol (Centers for Disease Control and Prevention, 2015). As we learned in Chapter 9, alcohol produces disinhibition which, in this case, can result in a shift from someone considering suicide to actually going through with it. This obviously makes alcohol consumption among those struggling with depression especially concerning.

**Review!** Disinhibition consists of a weakening of behavioral control that manifests as poor risk assessment, engagement in dangerous behavior, and impulsivity. Impulsivity consists of decision making without reflecting adequately on the consequences of those decisions (Chapter 9).

Across age groups, the prevalence of depression appears to be relatively balanced, as shown in Figure 13.1 (Kessler et al., 2005). Yet, we do find high rates of depression among the elderly, and twice as many suicides occur among the elderly compared to other adult groups. We also find high rates of depression, 17 percent, among those with Alzheimer's disease. Most elderly receive a diagnosis of depression from their primary doctors. Studies find, however, that most primary care doctors fail to make a diagnosis of depression for their elderly patients, and when a diagnosis is made, their doctors prescribe incorrect treatments (Alexopoulos, 2005).

A potential reason for depression in some elderly individuals may be poor blood flow to the brain. In advanced age, the vasculature throughout the body, including the brain, tends to harden and become less permeable to blood flow, which is critical for maintaining brain activity. In such a state, reduced brain activity may contribute to a depressed mood. The term for depressed symptoms associated with poor blood flow in the brain is called **vascular depression** (Alexopoulos et al., 1997).

**Vascular depression**
Depressed symptoms associated with poor blood flow in the brain

Just as we find a high prevalence of depression, we also find a high number of antidepressant prescriptions. In fact, the CDC states that antidepressants are the third most prescribed drugs among those 12 and older in the United States and the most prescribed drug among those between 18 and 44 years of age. Women are more than twice as likely to take antidepressant drugs as men, and more than one in five women ages 40 to 59 take antidepressant medications. In addition to the high frequency of being prescribed antidepressant drugs, most patients take these medications for at least two years (Pratt, Brody, & Gu, 2011).

## STOP & CHECK

1. Women are more likely to be diagnosed with major depressive disorder, but men are more likely to commit _____.
2. Despite a high prevalence of depression and a greater likelihood of successfully committing suicide, _____ individuals seldom receive a depression diagnosis from a mental health professional.
3. _____ depression refers to depressed symptoms associated with poor blood flow in the brain.

1. suicide 2. elderly 3. Vascular

### Neuroimaging Techniques and Functional Differences in Depression

Structural abnormalities in depression involve the amygdala, hippocampus, prefrontal cortex, and nucleus accumbens, among other structures (**Table 13.2**). The *amygdala*, a brain structure that mediates feelings of fear and aggression, appears overactive in depression. Using positron emission tomography (PET), Drevets and colleagues showed that individuals with depression exhibit increased cerebral blood flow in the left amygdala (Drevets et al., 1992). This same research group later found increased glucose uptake, a further indication that neuronal activity also occurs in the amygdala during depression (Drevets, Bogers, & Raichle, 2002).

**TABLE 13.2 Structures Implicated in Depression**

| Structure | Function in Depression |
|---|---|
| Amygdala | Increased activity |
| Hippocampus | Reduced volume |
| Prefrontal cortex | Reduced activity |
| Nucleus accumbens | Reduced volume; decreased activity |
| Basal ganglia | Reduced volume |

Magnetic resonance imaging (MRI) studies also reveal volume reductions in the hippocampus in depression. In an extensive review of imaging studies among depressed patients, Campbell, Marriott, Nahmias, and MacQueen (2004) found that the majority of studies reported these reductions in depressed individuals compared to non-depressed individuals. As presented later in this chapter, researchers have an interest in the hippocampus because of the ability of antidepressant drugs to promote neuron growth in this structure.

Although the amygdala appears overactive in depression, studies indicate underactivity in the left dorsal prefrontal cortex during depression (Savitz & Drevets, 2009). For example, in a study conducted by Drevets and colleagues (2002), PET assessments using F-18-fluorodeoxyglucose in unmedicated patients with unipolar depression consistently revealed decreased metabolism in the dorsal prefrontal cortex. The volume of gray and white matter also appears reduced in the left and right dorsal prefrontal cortex in depression and seems to be related to the severity of depression (Chen et al., 2007).

Volume reductions also suggest irregularities in the basal ganglia. The basal ganglia includes the nucleus accumbens, found in the ventral portion of the basal ganglia, and the other basal ganglia structures that facilitate movement. Although movement disorders are not a feature of depression, approximately half of all Parkinson's disease patients report a major depressive episode before the first occurrence of Parkinson's symptoms (Santamaria, Tolosa, & Valles, 1986).

Experimental deep brain stimulation treatments for depression also suggest an underactive nucleus accumbens in depression. In one such procedure, Schlaepfer and colleagues (2008) implanted brain electrodes into the nucleus accumbens of three patients. After surgery, activating the electrode reduced depression. In addition to these improvements, the patients spontaneously remarked about interest in doing something novel or something they had not done in many years. One patient, for example, said that she wanted to take up bowling again, and another patient wished to visit the Cologne Cathedral because it was nearby and he had never done so before.

Another potential contributor to depression may consist of the microbiome. As presented in Chapter 3's From Actions to Effects section, certain gut bacteria may influence levels of neurotransmitters in the central nervous system. Thus, depression patients might benefit from *psychobiotics*—probiotics that may facilitate a healthy microbiome for mental health.

## STOP & CHECK

1. The _____, a structure important for anxiety, is overactive in depression.
2. In depression, the left _____ appears to be underactive and to have reduced gray and white matter volume.
3. The volume reduction in the _____ is of particular interest because antidepressant drugs increase proliferation in this structure.

1. amygdala 2. dorsal prefrontal cortex 3. hippocampus

## Antidepressant Drugs

The first antidepressant drugs emerged during the 1950s when pharmacological treatments for mental illness were virtually unknown. The first antidepressant drug, *iproniazid (Marsilid)*, was developed for the treatment of tuberculosis in 1953 (Fox & Gibas, 1953). Loomer, Saunders, and Kline (1957) were the first to report a reduction in depressive symptoms among patients treated with iproniazid. Experimental animal findings showed that iproniazid reversed sedation and miosis produced by a drug called *reserpine*. (See **Box 13.1** for information on the use of animal behavior models to identify antidepressant drugs.)

# BOX 13.1

## ANIMAL BEHAVIORAL MODELS FOR IDENTIFYING ANTIDEPRESSANT DRUGS

An important challenge during drug development is an ability to behaviorally identify effective medications. Researchers have developed animal behavioral procedures that, although not resembling depression in a human, predict antidepressant efficacy. Common models used include the forced swim test, tail suspension test, and differential reinforcement of a low-rate 72-second task.

The *forced swim test* is an animal behavioral model of depression that measures the length of time a small animal, usually a rat or mouse, will swim in a cylinder of water. When the animal determines escape is impossible, it assumes a floating posture and only commits movements necessary to keep its head above water. Antidepressant researchers coin this floating posture as *behavioral despair*. The test arose from studies by Porsolt, Le Pichon, and Jalfre (1977) showing the successful identification of clinically proven antidepressant drugs. The *tail suspension test* is an animal behavioral model of depression that measures the length of time a mouse will struggle to escape while being briefly suspended by its tail. In this model, antidepressant treatment reduces the amount of time before an animal gives up struggling, or despairs (Cryan, Mombereau, & Vassout, 2005).

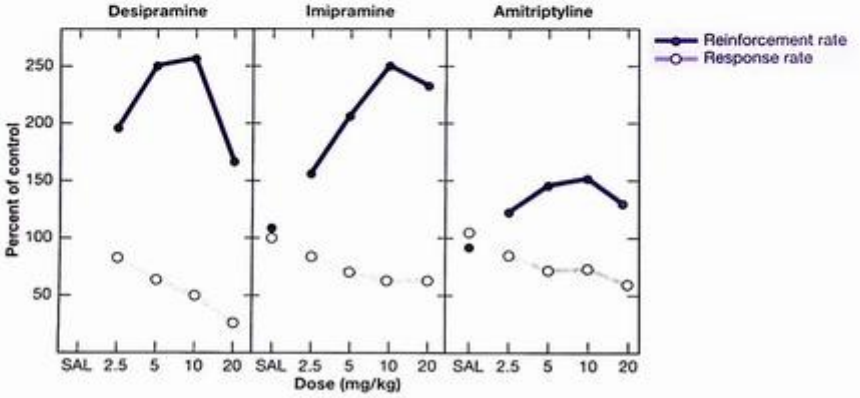
A *differential reinforcement of low-rate reinforcement schedule (DRL-72 sec)* requires a rat to withhold lever presses for food in an operant chamber until after 72 seconds have elapsed. If a rat presses the lever too soon, the 72-second counter resets. Only responses occurring after the full 72 seconds have passed result in food pellets. Thus, withholding responses for a period of time results in earning reinforcers. Antidepressant drugs, in this procedure, cause an increase in the reinforcement rate, defined as the number of food pellets earned over time, meaning that animals tend to wait longer before responding. In addition, response rates, defined as the number of responses that occur over a period of time, either increase or remain unchanged after acute administration of an antidepressant drug. We find many other drug classes capable of reducing responses in this procedure, but not without reducing overall response rates. Instead, antidepressant drugs enhance the likelihood of a rat waiting to respond until the right time, but they do not reduce responding overall. For example, benzodiazepine anxiolytic drugs (often referred to as tranquilizers) generally decrease both reinforcement and response rates. **Box 13.1 Figure 1** shows the effects of several tricyclic antidepressant effects on reinforcement and response rates in this task (O'Donnell, Marek, & Seiden, 2005).

*(Continued)*

(Continued)

**BOX 13.1 FIGURE 1** **Differential Reinforcement of Low-Rate, 72-Second Procedure for Identifying Antidepressant Drugs**

Antidepressant drugs improve the efficiency of responding in rats trained on a differential reinforcement of low-rate, 72-second operant schedule. Specifically, antidepressant drugs increase the reinforcement rate (shown by the solid symbols) and reduce the response rates (open symbols) compared to a control test (i.e., saline test). The data are graphed as percentages of control in order to easily show how each value can be compared to the control tests.




*Source:* Adapted from J. M. O'Donnell and L. S. Seiden (1983).

As was learned later, reserpine served to deplete the brain of monoamine neurotransmitters by irreversibly blocking transporters for synaptic vesicles (Carlsson, Lindqvist, & Magnusson, 1957; Holzbauer & Vogt, 1956; Viveros, Arqueros, Connett, & Kirshner, 1969). This action subsequently leads to catabolism (i.e., enzymatic breakdown of a molecule) of these neurotransmitters. The irreversible blockage of transporters on synaptic vesicles prevents the storage of any newly synthesized neurotransmitters. As a result, newly synthesized neurotransmitters largely become catabolized before escaping the axon terminal (Pletscher, Shore, & Brodie, 1955). Early case reports in fact described a mental depression occurring from long-term treatment with reserpine (Freis, 1954). Thus, as noted earlier, reserpine served as an early model that helped to discover some of the first antidepressant drugs.

Another critical development stemming from studies on reserpine involved understanding the role that monoamine depletion played in Parkinson's disease (a disorder we now link directly to dopamine depletion). During studies in the 1950s, researchers found that reserpine depleted norepinephrine in the brain (Carlsson, 2001; Holzbauer & Vogt, 1956). To determine if norepinephrine depletion might account for the sedation and loss of muscle movement caused by reserpine, Carlsson and colleagues administered a precursor for norepinephrine synthesis: levodopa. They reported their findings in 1957, stating that sedated rabbits woke up after treatment with levodopa, and they linked these effects to norepinephrine (recall that dopamine had yet to be identified as a neurotransmitter in the brain at this time) (Carlsson et al., 1957). Oliver Sacks famously wrote of levodopa treatment in patients exhibiting catatonic-like behavior from encephalitis lethargica in his book *Awakenings* (1973), and you can see these accounts dramatized in the 1990 movie of the same title. Thus, studies on reserpine led to a greater understanding of neurotransmission in the brain and helped to form theories about the causes of mental and neurological disorders.

Since these early days of the psychopharmacology era, the pharmaceutical industry has developed dozens of different antidepressant medications that vary in their pharmacological actions, clinical efficacy, and adverse effects. We classify antidepressant drugs according to their pharmacological actions and chemical structures, which has led to the following categories: monoamine oxidase (MAO) inhibitors, tricyclic antidepressant drugs, selective serotonin reuptake inhibitors, serotonin–norepinephrine reuptake inhibitors, and atypical antidepressant drugs (**Table 13.3**). Largely because of the actions of reserpine and early MAO inhibitors, researchers developed the monoamine hypothesis of depression. The **monoamine hypothesis of depression** states that a monoamine deficiency causes depressive mood. Although more than half a century of research has passed since these first drugs came out, we still develop antidepressant drugs largely based on this hypothesis (Hillhouse & Porter, 2015).

**Monoamine hypothesis of depression**
Hypothesis stating that a monoamine neurotransmitter deficiency causes depressive mood

**Review!** Monoamine neurotransmitters consist of dopamine, norepinephrine, and serotonin (Chapter 3).

## Monoamine Oxidase Inhibitors

Researchers have discovered and named two types of MAO: $MAO_A$ and $MAO_B$. We find $MAO_A$ in the brain, peripheral nervous system, and the intestinal tract, whereas $MAO_B$ is found mainly in the brain and, to a lesser extent, in the peripheral nervous system. In the brain, $MAO_A$ resides in dopamine and norepinephrine neurons, and $MAO_B$ resides in serotonin and norepinephrine neurons (Mills, 1997).

*Iproniazid* became known as the first clinically used antidepressant drug among the MAO inhibitors. **MAO inhibitors** produce antidepressant effects by binding to MAO and preventing it from breaking down monoamine neurotransmitters, including serotonin, dopamine, and norepinephrine, as well as other monoamine compounds such as tyramine (**Table 13.4**). Depending on the particular drug, an MAO inhibitor may bind irreversibly or reversibly to MAO. For **irreversible MAO inhibitors**, the drug never releases from MAO. To make up for the loss of functional MAO

**MAO inhibitors**
Produce antidepressant effects by binding to MAO and preventing it from breaking down monoamine neurotransmitters

**Irreversible inhibitors**
Antidepressant drugs that irreversibly bind to MAO

**TABLE 13.3 Selected Antidepressant Drugs**

| Monoamine Oxidase Inhibitors | Tricyclic Antidepressant Drugs | Selective Serotonin Reuptake Inhibitors | Serotonin–Norepinephrine Reuptake Inhibitors | Atypical Antidepressant Drugs |
|---|---|---|---|---|
| Iproniazid (*Marsilid*) | Amitriptyline (*Elavil*) | Citalopram (*Celexa*) | Duloxetine (*Cymbalta*) | Agomelatine (*Valdoxan* or *Thymanax*) |
| Moclobemide (*Aurorix*) | Clomipramine (*Anafranil*) | Dapoxetine (*Priligy*) | Desvenlafaxine (*Prestiq*) | Bupropion (*Wellbutrin*) |
| Phenelzine (*Nardil*) | Desipramine (*Pertofrane*) | Escitalopram (*Lexapro*) | Levomilnacipran (*Fetzima*) | Esketamine (*Spravato*) |
| Selegiline (*Emsam*) | Imipramine (*Tofranil*) | Fluoxetine (*Prozac*) | Milnacipran (*Ixel*, *Savella*) | Mirtazapine (*Remeron*) |
| Tranylcypromine (*Parnate*) | Nortriptyline (*Pamelor*) | Fluvoxamine (*Luvox*) | Venlafaxine (*Effexor*) | Trazodone (*Desyrel*) |
| | | Indalpine (*Upstene*) | | Vortioxetine (*Brintellix* or *Trintellix*) |
| | | Paroxetine (*Paxil*) | | |
| | | Sertraline (*Zoloft*) | | |

**TABLE 13.4 Pharmacological Actions of Antidepressant Drugs on Neurotransmission**

| Antidepressant Drug Class | Pharmacological Actions on Neurotransmission | Neurotransmitter Levels |
|---|---|---|
| MAO inhibitors | Inhibit MAO, preventing catabolism of monoamine neurotransmitters | Increase dopamine, norepinephrine, and serotonin |
| Tricyclic antidepressant drugs | Inhibit reuptake of serotonin and norepinephrine; bind to various receptors | Increase serotonin and norepinephrine levels |
| Selective serotonin reuptake inhibitors (SSRIs) | Inhibit reuptake of serotonin | Increase serotonin levels |
| Serotonin–norepinephrine reuptake inhibitors (SNRIs) | Inhibit reuptake of serotonin and norepinephrine | Increase serotonin and norepinephrine levels |
| Atypical antidepressant drugs | Vary depending on the particular drug | Generally increase levels of one or more monoamine neurotransmitters |
| Psychedelic antidepressant drugs | Act through psychedelic drug mechanisms, such as antagonism of NMDA receptors or activation of serotonin receptors | May increase dopamine and glutamate levels in the prefrontal cortex |

enzymes, neurons synthesize more MAO. For **reversible MAO inhibitors**, the drug either temporarily binds to MAO or other compounds such as tyramine to displace the drug from MAO.

An adverse effect termed the *cheese reaction* limited the use of the first MAO inhibitors for treating depression. Clinicians characterize the **cheese reaction** as overactivation of the sympathetic nervous system because of MAO inhibition causing increased heart rate, hypertension (high blood pressure), sweating, and inhibited digestion. In fact, when severe enough, we refer to the high degree of hypertension occurring here as a *hypertensive crisis*. This reaction occurs when MAO inhibition increases the levels of norepinephrine and tyramine. Norepinephrine activates $\beta_1$ adrenoceptors on cardiac tissue, causing increased heart rate and strength of muscle contractions. Tyramine, which does not cross the blood–brain barrier, likely enhances these effects by displacing stored norepinephrine in sympathetic nervous system neurons, causing some norepinephrine to leak from axon terminals and contribute to the activation of $\beta_1$ adrenoceptors (Axelrod, Gordon, Hertting, Kopin, & Potter, 1962; Graefe, Bossle, Wolfel, & Burger, 1999).

Modern MAO inhibitors reduce, but do not eliminate, the risk of a cheese reaction. The first type of modern MAO inhibitors were selective inhibitors of $MAO_B$. **Selective $MAO_B$ inhibitors**, such as *selegiline (Emsam)*, have a greater affinity for $MAO_B$ than $MAO_A$, thereby engendering most of their effects through acting in the brain. Selegiline also can be administered through a skin patch, allowing the drug to bypass the intestinal tract, where it would otherwise cause some buildup of tyramine.

The second type of modern MAO inhibitors are reversible inhibitors of $MAO_A$ (abbreviated as RIMA). **RIMA drugs** selectively inhibit $MAO_A$ but allow for displacement from $MAO_A$ by tyramine. By allowing $MAO_A$ to break down tyramine, RIMA provides patients with a lower risk of a cheese reaction. *Moclobemide (Aurorix, Manerix)* is a RIMA clinically available for depression in Canada and Europe, but the weak efficacy of the drug failed to gain it FDA approval in the United States (Youdim, 2006).

**Reversible MAO inhibitors**
Antidepressant drugs that either temporarily bind to MAO or allow other compounds to displace the drug from MAO

**Cheese reaction**
Overactivated sympathetic nervous system functioning because of MAO inhibition that leads to increased heart rate, hypertension, sweating, and inhibited digestion

**Selective $MAO_B$ inhibitors**
Antidepressant drugs that primarily inhibit $MAO_B$ enzymes and exhibit weaker inhibition of $MAO_A$ enzymes

**RIMA drugs (reversible inhibitors of $MAO_A$)**
Antidepressant drugs that selectively inhibit $MAO_A$ but allow for displacement from MAO, by tyramine

## STOP & CHECK

1. What was the first antidepressant drug, iproniazid, actually developed for?
2. A deficiency of dopamine, norepinephrine, or serotonin is the basis for the _____ hypothesis of depression.
3. $MAO_A$ is found in the intestinal tract, peripheral nervous system, and the brain, whereas $MAO_B$ is primarily found in the _____.
4. Why might a reversible $MAO_A$ inhibitor be preferable to an irreversible MAO inhibitor to treat depression?

1. tuberculosis 2. monoamine 3. brain 4. A reversible MAO$_A$ inhibitor enhances levels of the monoamines dopamine, norepinephrine, and serotonin, but has a low cheese reaction risk because it can be displaced by tyramine. An irreversible MAO inhibitor causes a buildup of tyramine, which contributes to sympathetic nervous system activation and the subsequent cheese reaction.

## Tricyclic Antidepressant Drugs

**Tricyclic antidepressant drugs**
Antidepressant drugs that inhibit the reuptake of norepinephrine and serotonin and function as antagonists for various receptors

**Tricyclic antidepressant drugs** inhibit reuptake of norepinephrine and serotonin and function as antagonists for various receptors, often including muscarinic acetylcholine receptors (Table 13.4) (Lenox & Frazer, 2002). Tricyclic refers to three connected benzene rings shared by drugs in this category. Chemists developed the first tricyclic antidepressant drug, imipramine, in an attempt to produce drugs similar to the first antipsychotic drug *chlorpromazine (Thorazine)* for the purpose of treating schizophrenia (Davis, 2006). Although failing to effectively treat schizophrenia, clinicians noticed improvements in mood, prompting clinical testing for depression instead. In particular, imipramine appeared most effective among patients with greater severity in depression (Kuhn, 1958).

*Tricyclic* antidepressant drugs provide certain pharmacological actions similar to MAO but do so through a different mechanism. Tricyclic antidepressants achieve elevations in serotonin and norepinephrine levels by inhibiting reuptake at membrane transporters, rather than through inhibiting catabolism of neurotransmitters as MAO inhibitors do. This also avoids a cheese reaction from occurring with tricyclic antidepressant drugs, although these drugs have unique adverse effects of their own.

A number of adverse effects occur from tricyclic antidepressant drugs binding to various receptors in the nervous system. Most tricyclic antidepressant drugs serve as antagonists for cholinergic muscarinic receptors. In the parasympathetic nervous system, blocking muscarinic receptors causes dry mouth, dry eyes, constipation, urinary retention (from a lack of bladder relaxation), and various other effects related to blocking neurotransmission in this system. As a result of dry eyes, blurred vision also may occur. In the brain, blocking muscarinic receptors can also lead to impairments in memory and cognitive functioning (Lenox & Frazer, 2002).

Many tricyclic antidepressants also block $\alpha_1$ adrenoceptors, causing vasodilation and effects similar to orthostatic *hypotension*, low blood pressure typically noted by an individual feeling lightheaded or dizzy when suddenly standing up. Greater blood flow to the head resulting from vasodilation may also cause headaches and the feeling of a "head rush." Many of these drugs act as histamine $H_1$ receptor antagonists, which cause sedative effects just as antihistamine cold medicines do. In addition, tricyclic antidepressants are known to cause weight gain, which can lead to a variety of health concerns, including type II diabetes (Brown, Majumdar, & Johnson, 2008; Lenox & Frazer, 2002). Keeping all of these adverse effects in mind, it's not surprising that patients prescribed tricyclic antidepressants report feeling "drug laden," which can reduce *patient compliance* (i.e., the likelihood of a patient continuing to take the prescribed medication) (Lenox & Frazer, 2002).

## STOP & CHECK

1. Tricyclic antidepressants reduce depressive symptoms by preventing the reuptake of _____ and _____.
2. What effect might the adverse effects of tricyclic antidepressant drugs have on patient compliance?

1. serotonin, norepinephrine 2. These adverse effects decrease the likelihood of patients reliably taking these medications. Parasympathetic nervous system inhibition can cause a number of boltersome effects, including dry mouth, blurred vision, constipation, cognitive disruption, and urinary retention. In particular, weight gain often deters patient compliance.

**Review!** Adrenoceptors are the receptors for the neurotransmitter norepinephrine (Chapter 3).

## Selective Serotonin Reuptake Inhibitors (SSRIs)

The pharmacological actions of tricyclic antidepressant drugs established a directed effort to develop drugs that selectively inhibited the reuptake of serotonin or norepinephrine. Based on these pharmacological actions and other experimental support for the specific influence of serotonin on mood, Arvid Carlsson worked with Astra Pharmaceuticals to develop *zimelidine (Zelmid)* for the treatment of depression (Shorter, 1997). Thus, zimelidine was the first selective serotonin reuptake inhibitor. A **selective serotonin reuptake inhibitor (SSRI)** elevates serotonin levels by blocking reuptake through serotonin membrane transporters (Table 13.4). Beginning in 1981, zimelidine was marketed in Europe for a limited time, but was abruptly withdrawn from the market due to damaging myelin sheathing around central and peripheral nervous system axons.

Researchers at Eli Lilly discovered a safer SSRI—*fluoxetine*—which is best known by its trade name *Prozac*. Fluoxetine met FDA approval for the treatment of depression in 1987. It was found to be generally safer than MAO inhibitors and tricyclic antidepressant drugs, and fluoxetine became one of the most prescribed drugs in history (Shorter, 1997).

Because of their perceived safety, SSRIs have been prescribed for depression in teens and children. However, in 2005 the FDA issued a **black box warning** (or **boxed warning**), a warning on the package insert given a black border around it to draw special attention to it, that SSRIs increased suicide risk in teens and children (Food and Drug Administration, 2005). This warning was based on a review of published clinical studies in teens that together indicated a higher suicide rate (four percent) compared to placebo-treated patients (two percent). This warning does not ban the use of these medications in children and teens, but rather, indicates that physicians must carefully monitor suicidal tendencies after prescribing these medications.

We find other significant concerns for SSRIs as well. They may cause **serotonin syndrome**, a life-threatening condition characterized by agitation, restlessness, disturbances in cognitive functioning, and possibly hallucinations. This syndrome is usually avoided by taking low or moderate doses of an SSRI, although a drug reaction with another serotonin compound, such as a different antidepressant drug or lithium, can increase the risk of serotonin syndrome (Sternbach, 1991).

Just as taking SSRIs might lead to serotonin syndrome, abrupt withdrawal from SSRI treatment may cause serotonin *discontinuation* syndrome. The **serotonin discontinuation syndrome** is characterized by sensory disturbances, sleeping disturbances, disequilibrium, flu-like symptoms, and gastrointestinal effects. Those seeking to discontinue SSRI use must slowly wean themselves from the medication by reducing the amount taken over time (Sternbach, 1991).

Elevations in serotonin levels are likely to cause **sexual side effects**, including erectile dysfunction, inability to achieve orgasm, and loss of sexual drive. In a survey asking patients taking SSRIs to determine how they felt compared to their usual state, the majority of those surveyed reported far less interest in having sex and less pleasure during sex (Opbroek et al., 2002; see Figure 13.2). These side effects

**Selective serotonin reuptake inhibitor (SSRI)**
Antidepressant drug that elevates serotonin levels by blocking reuptake through serotonin membrane transporters

**Black box warning (or boxed warning)**
A warning on a drug's package insert given a black border around it to draw special attention to it

**Serotonin syndrome**
Antidepressant-drug-induced life-threatening condition characterized by agitation, restlessness, disturbances in cognitive functioning, and possibly hallucinations

**Serotonin discontinuation syndrome**
Syndrome caused by abrupt withdrawal of an antidepressant drug, resulting in sensory disturbances, sleeping disturbances, disequilibrium, flu-like symptoms, and gastrointestinal effects

**Sexual side effects**
Sexual dysfunction, including erectile dysfunction, inability to achieve orgasm, and loss of sexual drive caused by antidepressant drugs

negatively affect one's quality of life and contribute to poor patient compliance with these medications.

**Emotional blunting (or affective blunting)** Feelings of emotional detachment along with experiencing reduced positive and negative emotions

An often-overlooked adverse effect of SSRIs is a condition referred to as *emotional blunting*. **Emotional blunting** (or **affective blunting**) consists of feelings of emotional detachment along with experiencing reduced positive and negative emotions. Patients describing these reduced emotional feelings insist that they result from the medication, rather than depression, and use labels such as "dulled," "flattened," or "numbed" to express how they feel (Price, Cole, & Goodwin, 2009). Thus, a person with emotional blunting may not seem particularly sad or happy, just neutral.

We gain some insight into emotional blunting among patients treated with SSRIs from a survey conducted by Opbroek and colleagues (2002). The patients studied consisted of those reporting sexual dysfunction and in the course of evaluation were surveyed on other items to determine how they felt compared to their "usual" state. **Figure 13.2** provides their average responses. In particular, we find a substantial reduction in sexual interest and enjoyment, as reported above, and many of the participants reporting a lower ability to cry, become angry, care about the feelings of others, and feel creative.

In addition to feeling emotionally blunted, patients may also have a hard time identifying the actual emotions they feel. Kajanoja, Scheinin, Karukivi, Karlsson, and Karlsson (2018) reviewed data from a population of SSRI-treated depression patients who were given a questionnaire to evaluate alexithymia, a condition characterized by difficulty in identifying emotions. Items on the questionnaire included confusion about identifying their own emotions, an inability to interpret physical sensations, or an inability to link an upsetting feeling with anger, sadness, or fear. The study found that SSRI-treated participants scored significantly poorer than non-SSRI-treated participants on this questionnaire, suggesting that emotional blunting coincides with difficulty interpreting emotions.

## STOP & CHECK

1. SSRIs enhance serotonin levels by blocking _____.
2. High doses of an SSRI may cause _____, which is characterized by agitation, restlessness, cognitive disruption, and hallucinations.
3. Abrupt withdrawal from SSRI treatment causes _____.

1. serotonin transporters 2. serotonin syndrome 3. serotonin discontinuation syndrome

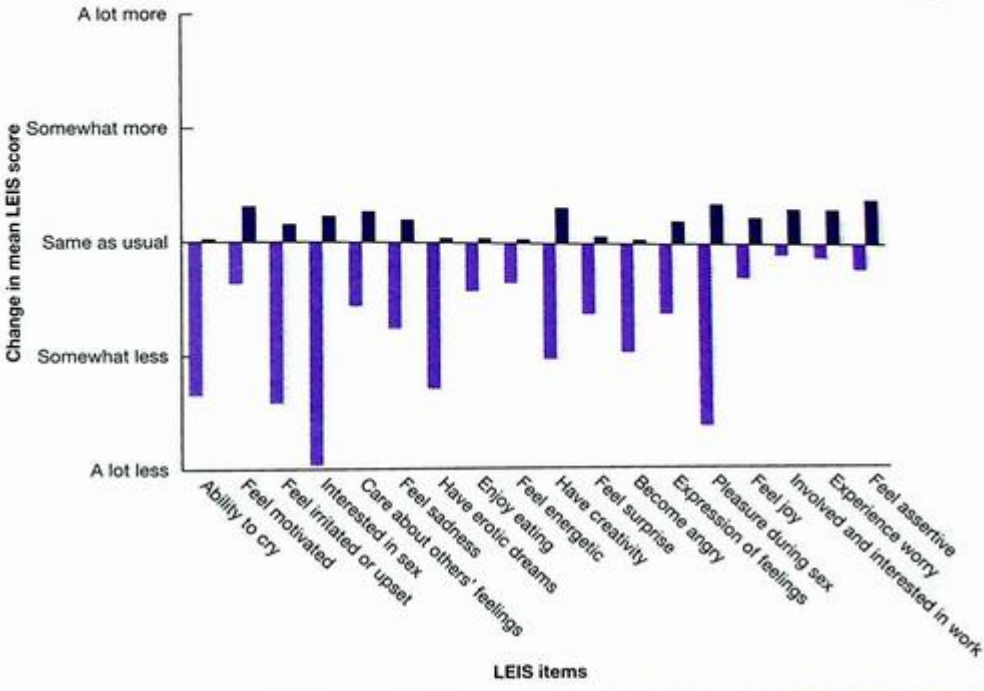
**Serotonin–norepinephrine reuptake inhibitors (SNRIs) (or dual serotonin and norepinephrine reuptake inhibitors)** Antidepressant drugs that enhance levels of serotonin and norepinephrine by blocking serotonin and norepinephrine membrane transporters

## Serotonin–Norepinephrine Reuptake Inhibitors (SNRIs)

**Serotonin–norepinephrine reuptake inhibitors (SNRIs)**, which are also called **dual serotonin and norepinephrine reuptake inhibitors**, enhance levels of serotonin and norepinephrine by blocking serotonin and norepinephrine membrane

**FIGURE 13.2 SSRI Treatment and Emotional Blunting**

Average scores on a questionnaire asking SSRI-treated patients how they currently felt compared to their "usual" state.



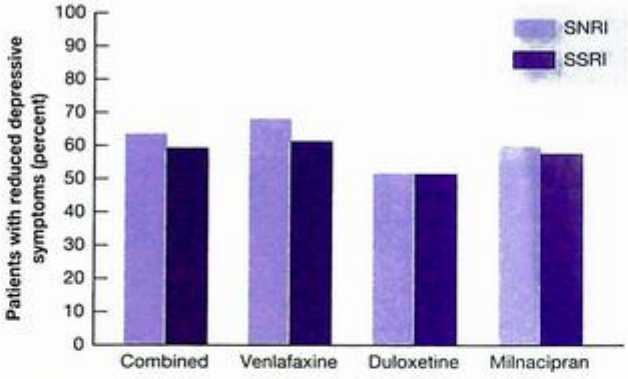

*Source:* Opbroek, A., Delgado, P. L., Laukes, C., McGahuey, C., Katsanis, J., Moreno, F. A., & Manber, R. (2002). Emotional blunting associated with SSRI-induced sexual dysfunction. Do SSRIs inhibit emotional responses? *International Journal of Neuropsychopharmacology, 5*(2), 147–151.

transporters. The push for new antidepressant drugs led to the development of *venlafaxine* (*Effexor*), the first of the class of SNRIs. Venlafaxine (*Effexor*) received FDA approval for the treatment of depression in 1993. Venlafaxine and other SNRIs, such as *duloxetine (Cymbalta)*, are at least as effective as SSRIs for the treatment of depression, and some studies conclude that SNRIs are more effective. As inhibitors of serotonin reuptake, they share the same adverse effects as SSRIs.

Papakostas, Thase, Fava, Nelson, and Shelton (2007) conducted a meta-analysis on clinical depression studies that used either an SSRI or an SNRI to determine which class was the most effective. The literature review was extensive, including more than 90 trials and more than 17,000 patients. In each comparison, an SNRI produced a slightly greater improvement than an SSRI. The effects were modest, but consistent (**Figure 13.3**).

**FIGURE 13.3 SNRIs Versus SSRIs for Treatment of Depression**

According to a review of antidepressant clinical trials, SNRIs (lighter bars) consistently reveal greater improvements in depressive symptoms than SSRIs (darker bars). However, these differences were seldom robust. The particular SNRI studied is noted on the *x*-axis, and the "combined" label refers to all studies combined.




*Source:* Adapted from Papakostas et al. (2007).

**Fibromyalgia syndrome**
A musculoskeletal disorder characterized by widespread pain occurring as muscle tenderness in addition to other symptoms including fatigue, disrupted sleep, and depressed mood

Another disorder linked, at least in part, to stress is fibromyalgia. **Fibromyalgia syndrome** is a musculoskeletal disorder characterized by widespread pain occurring as muscle tenderness in addition to other symptoms, including fatigue, disrupted sleep, and depressed mood (Abeles, Pillinger, Solitar, & Abeles, 2007). The disorder occurs in 3.4 percent of women and 0.5 percent of men in the United States (Wolfe, Ross, Anderson, Russell, & Hebert, 1995). The cause of fibromyalgia remains unknown but likely involves multiple interaction mechanisms, including sensitization of pain pathways; reduced neurotransmission of monoamine neurotransmitters; and a current or previous mental disorder, such as depression or anxiety (Abeles et al., 2007). Pain levels, which fluctuate throughout the day, are particularly worsened by stress (Fischer et al., 2016).

Both norepinephrine and serotonin, among many other neurotransmitters, have been shown to modulate pain signalling (Millan, 2002). The notion that diminished norepinephrine and serotonin levels in fibromyalgia may contribute to increased pain sensitivity led to testing different types of antidepressant drugs. Arnold and colleagues (2004) reported one of the major findings in this area—that the SNRI duloxetine reduced pain and other features of fibromyalgia in both depressed and non-depressed patients. Antidepressant drugs, especially those of the SNRI class, have become the first-line pharmacological treatments for fibromyalgia. Aside from antidepressant drugs, the drug *pregabalin (Lyrica)* also is used (Crofford et al., 2005). Unlike the antidepressant drugs, pregabalin produces CNS depressant effects through inhibition of calcium channels, thereby attenuating pain signals to the brain as well as potentially reducing stress (Taylor, Angelotti, & Fauman, 2007).

Non-pharmacological treatment strategies include physical therapy, relaxation techniques, cognitive-behavioral therapy, and exercise (Rossy et al., 1999).

## Atypical Antidepressant Drugs

**Atypical antidepressant drugs** reduce depression through mechanisms that differ from those of other antidepressant classifications. They are neither MAO inhibitors nor tricyclic antidepressants. Nor do atypical antidepressant drugs selectively block either serotonin reuptake, norepinephrine reuptake, or both. Thus, this category is a bit of a catch-all for antidepressant drugs that do not fit into other antidepressant drug categories. All atypical antidepressant drugs currently available alter neurotransmission for one or more monoamine neurotransmitters, with the exception of brexanolone, described later.

**Atypical antidepressant drugs**
Antidepressant drugs that reduce depression through mechanisms that differ from those of other antidepressant classifications

One of the most prescribed atypical antidepressant drugs is *bupropion (Wellbutrin)*. Bupropion is a reuptake inhibitor for norepinephrine and dopamine and therefore is unique among the antidepressants for its lack of serotonin elevation. Given the lack of serotonin effects, bupropion does not carry a risk for serotonin syndrome, and it does not have a risk of sexual side effects (Ascher et al., 1995).

Questions exist about the efficacy of the atypical antidepressant drug *reboxetine*, which functions as a selective norepinephrine reuptake inhibitor. Clinical study data released in the 1990s indicated superior, long-term antidepressant effects and a low rate of adverse effects compared to placebo (Burrows, Maguire, & Norman, 1998). Such findings allowed approval of reboxetine for use in Europe, but the FDA denied approval based on unpublished clinical data that reboxetine's drug maker, Pfizer, was required to release under U.S. law (but not required to release in Europe) (Szalavitz, 2010). A study examining these unpublished data together with published data concluded that reboxetine not only lacked clinical efficacy for depression, but that the unpublished data revealed greater adverse effects from the drug than published data had indicated (Eyding et al., 2010).

A more recently developed atypical antidepressant drug is *vortioxetine (Brintellix, Trintellix)*, which met FDA approval in 2013. Like SNRIs, vortioxetine inhibits serotonin reuptake and, to a lesser extent, also inhibits norepinephrine reuptake (Bang-Andersen et al., 2011). Researchers classified vortioxetine as an atypical antidepressant because of its additional effects at a host of serotonin receptors, serving as an antagonist for some serotonin receptors (e.g., $5\text{-HT}_3$) and an agonist for other receptors (e.g., $5\text{-HT}_{1A}$) (Sanchez, Asin, & Artigas, 2015).

The atypical antidepressant drug trazodone (*Desyrel, Oleptro*, among other names) has been available in the United States since 1981. Like vortioxetine, trazodone inhibits serotonin reuptake and serves as an antagonist for multiple serotonin receptors, including $5\text{-HT}_{2A}$ and $5\text{-HT}_{2C}$, and acts as an agonist for $5\text{-HT}_{1A}$ receptors. Given the pharmacological actions of trazodone and vortioxetine, these drugs are also noted as belonging to a class of antidepressants called *serotonin antagonist and reuptake inhibitors*, referred to by the acronym SARI. In addition to acting at serotonin receptors, trazodone acts as an antagonist for $\alpha_1$ adrenoceptors for norepinephrine and as an antagonist for histamine $H_1$ receptors. The drug's antihistamine actions account for its hypnotic (i.e., sleep-inducing) effects, and we find trazodone commonly prescribed off-label for treating insomnia (Settimo & Taylor, 2018).

Another atypical antidepressant drug is *agomelatine (Valdoxan* or *Thymanax)*, a drug approved for use in Europe but not currently approved by the FDA for use in the United States. Agomelatine acts as an agonist for melatonin receptors and an antagonist for serotonin 5-$HT_{2C}$ receptors. Studies find that agomelatine restores sleep patterns among study participants with major depressive disorder, likely by acting on melatonin receptors. Researchers also report reduced depression among agomelatine-treated patients compared to those treated with placebo. While not serving as a reuptake inhibitor for monoamine neurotransmitters, antagonism of 5-$HT_{2C}$ receptors may produce increased levels of dopamine, as discussed later in this chapter. Consistent with these pharmacological actions, clinical trials with agomelatine did not find increased rates of sexual dysfunction (Sansone & Sansone, 2011).

## Atypical Antidepressant Drugs: Psychedelics

**Psychedelic antidepressant drug**
An approved drug for the treatment of depression that can produce a psychedelic experience

An emerging class of antidepressant drugs comes from known psychedelic drugs. A **psychedelic antidepressant drug** is an approved drug for the treatment of depression that can produce a psychedelic experience. Psychedelic drugs presently approved or in clinical trials share a number of features (**Table 13.5**). They feature a strong likelihood of a psychedelic experience immediately after administration. Clinical improvements also occur rapidly, generally within a day of drug administration. Often, these effects show as soon as the psychedelic experience ends. Psychedelic antidepressant drugs only require infrequent administrations. Also, these drugs exhibit long-lasting effects, normally weeks after a single administration.

The first U.S. FDA-approved psychedelic antidepressant drug is *esketamine*, sold under the brand name *Spravato*. Esketamine is the "s" enantiomer of ketamine. The drug comes in the form of a nasal spray and the FDA approved esketamine to be taken with an oral antidepressant drug for depressed patients found to be treatment-resistant. Moreover, in keeping with the clinical investigations on ketamine, the recommendation includes taking the drug infrequently—twice per week at first and later once every other week or two for maintenance. Due to abuse concerns and occurrence of acute psychedelic effects, patients must administer the drugs in a clinician's office and the drug cannot be taken home (Food and Drug Administration, 2019).

**TABLE 13.5 Characteristics of Psychedelic Drugs for Treating Depression**

| Effect | Characteristics |
|---|---|
| Psychedelic experience | May occur acutely after administration |
| Rapid onset for antidepressant effects | Clinical improvement for depression typically occurs within a day of drug administration, often immediately after the psychedelic experience ends |
| Infrequent administrations | Each drug administration is days or weeks apart |
| Long-lasting antidepressant effects | Reductions in depression found weeks or months following antidepressant treatment |

## Drug Profile: esketamine

| | |
|---|---|
| Brand name | *Spravato* |
| Properties | Antagonist for glutamate NMDA receptors |
| Uses | Used for treatment-resistant depression |

Ketamine was first introduced in Chapter 12, where it was described as a dissociative anesthetic and glutamate NMDA receptor antagonist. Ketamine's antidepressant effects were first reported by Berman and colleagues (2000), who assessed intravenous infusion of a low ketamine dose to seven volunteers with major depressive disorder. Patients exhibited an immediate reduction in depressive symptoms that lasted as long as three days after treatment. A subsequent study found that ketamine's antidepressant effects lasted as long as one week (Zarate et al., 2006), and many other short-term studies since then have confirmed that ketamine serves as a robust and rapid-acting antidepressant drug in patients with treatment-resistant depression. A long-term study, consisting of 16 weeks, found that esketamine prevented relapse among treatment-resistant depressed patients who were also taking an oral antidepressant drug (Daly et al., 2019).

## STOP & CHECK

1. How do the efficacy and safety of SNRIs compare to SSRIs?
2. What is atypical about atypical antidepressant drugs?

1. SNRIs are at least as effective for depression as SSRIs, and many clinical studies indicate a modestly greater efficacy by SNRIs. Both SNRIs and SSRIs have similar adverse effects. 2. The mechanisms of action for atypical antidepressant drugs differ from those of other antidepressant drug classes.

**Review!** Melatonin is a sleep-inducing hormone that plays an important role in circadian rhythm, our natural sleep cycle (Chapter 3).

## Limitations in Antidepressant Drug Effectiveness and Development

Although antidepressant drug classes differ pharmacologically and have unique adverse effects, they share many of the same limitations for treating depression. We consider four issues in this section: length of response time, treatment resistance,

strong placebo effects in clinical trials, and depression severity. The "From Actions to Effects" section later in this chapter also considers pharmacogenetic factors in antidepressant response.

## Length of Response Time

All antidepressant drugs have a lengthy response time. For those who eventually respond to antidepressant drugs, clinically significant effects occur after two weeks of treatment and generally show full effects after four weeks. If patients fail to respond sufficiently after four weeks, then the likelihood of successful treatment with the drug diminishes. The long response time is particularly concerning when treating patients with a high risk of suicide (Nierenberg et al., 2000).

## Treatment Resistance

Many patients may fail to respond adequately to antidepressant treatment. Fava and Davidson (1996) estimated that between 29 and 46 percent of patients fail to fully recover with antidepressant drug treatment. In these cases, clinicians may increase the dose of the SSRI, add another medication (see following), or switch altogether to a different antidepressant drug. We identify an individual as having **treatment-resistant depression** after successive failed attempts to significantly reduce depressive symptoms by antidepressant medication, including a treatment course with an SSRI (Trivedi et al., 2006).

**Treatment-resistant depression**
Diagnosis made after successive failed attempts to significantly reduce depressive symptoms

## Placebo Effects in Clinical Studies

Placebo effects present an important issue for drug developers during clinical trials for antidepressant drugs. To gain governmental approval, novel antidepressant drugs must be tested in clinical trials that compare the novel drug to placebo. When conducting clinical trials with antidepressant drugs, a clinically significant improvement often occurs in placebo-treated patients. This requires a novel antidepressant drug to produce clinical effects that significantly exceed those found with placebo. Given these strong placebo effects combined with the cautious nature of clinical drug testing, researchers may fail to find clinically significant antidepressant drug effects.

The placebo effect is a criticism of antidepressant efficacy. As raised by Kirsch (2014) and many others, the placebo effect indicates a lack of clinical efficacy by many antidepressant drugs brought to clinical trials. According to an analysis conducted of FDA clinical trials, only 43 percent reported clinical improvements beyond those observed from placebo. Moreover, the observation that non-antidepressant drugs occasionally produced supposedly antidepressant effects over placebo in some trials has led to the criticism that perhaps any perceived drug effect by a study participant was interpreted as an antidepressant effect, thus resulting in reduced rates of depression. Said another way, an antidepressant drug might actually be a placebo (Kirsch, 2014).

In an unexpected way, the lack of efficacy by reboxetine (mentioned earlier) might serve as a counterargument to claims that antidepressant drugs are simply placebos. As noted earlier, unpublished clinical data revealed a lack of efficacy for depression,

but also higher rates of adverse effects. Thus, study participants found a lack of antidepressant efficacy despite experiencing clear drug effects (Szalavitz, 2010).

Along these lines, researchers have questioned the integrity of the "blind" in double-blind placebo-controlled studies. That is, placebo-treated patients may deduce their placebo treatment by the lack of drug effects, including side effects (Antonuccio, Danton, DeNelsky, Greenberg, & Gordon, 1999). During studies with tricylic antidepressant drugs, these studies received criticism for the lack of dry mouth and blurred vision found among placebo-treatment patients who may have expected to experience adverse effects or may have talked to study participants who received the active treatment. Breaking the blind, in turn, diminished any potential improvements in depression that might have occurred due to placebo alone.

To address concerns such as these, clinical trials may adapt an *active placebo*—a drug that produces side effects but not the targeted therapeutic effects. For active placebos for tricyclic antidepressant drugs, the active placebo usually consisted of an anticholinergic drug, such as atropine. In a review of studies that incorporated an active placebo for tricyclic antidepressant drugs, only two of the nine studies reviewed found the antidepressant drug superior to the active placebo (Moncrieff, Wessely, & Hardy, 1998). SSRIs typically lack anticholinergic effects and generally create fewer distinct adverse effects that may alert patients about a placebo treatment. Thus, active placebos for SSRIs may be unavailable.

## Depression Severity

The efficacy of antidepressant drugs may depend on the severity of depression a patient is suffering from. Numerous clinical trials have revealed the efficacy for antidepressant drugs for severe depression, rather than mild (or non-severe) depression, compared to placebo. Moreover, these studies included clinical trial data that had been submitted to the FDA, but not published (Khan, Leventhal, Khan, & Brown, 2002; Kirsch et al., 2008). On the other hand, other statistical analyses of these clinical data have revealed a clear advantage for using antidepressant drugs, compared to placebo, regardless of symptom severity (Fountoulakis, Veroniki, Siamouli, & Möller, 2013).

Another consideration is how antidepressant drug effects are measured in clinical trials. Hieronymus, Lisinski, Nilsson, and Ericksson (2019) speculate that lack of antidepressant drug effects for non-severe depression may concern the psychological instruments used for measuring depression. In particular, studies commonly use the Hamilton Depression Rating Scale, which consists of 17 items, including depressed mood, feelings of guilt, insomnia, suicide, and other features of depression, in which an assessor rates answers from zero to four based on severity (four is the highest level of severity). The sum of the items relates to the severity of depression (**Figure 13.4**).

Hieronymus and colleagues (2019) argue that non-severe depression leads to a low total score on this scale, as this scale better captures severe depression. Therefore, a lower total score on this rating scale for mild depression leaves little room for an antidepressant drug to reduce the score to the substantial degree needed to demonstrate statistical significance. Instead, these authors evaluate a subset of this scale, referred to as the Bech subscale, to focus on the following items: depressed mood, feelings of

## FIGURE 13.1 Hamilton Depression Rating Scale

The Hamilton Depression Rating Scale is commonly used to rate severity of depression. A clinician asks a patient questions that allow the clinician to score each item, with higher values indicating greater severity. A total score is gathered by adding up the values across the items. Total scores of seven and lower do not indicate a state of depression, whereas scores of 20 and higher indicate at least moderate depression.

### Hamilton Depression Rating Scale (HDRS)

PLEASE COMPLETE THE SCALE BASED ON A STRUCTURED INTERVIEW

Instructions: For each item select the one "cue" which best characterizes the patient. Be sure to record the answers in the appropriate spaces (positions 0 through 4).

---

**1 DEPRESSED MOOD** *(sadness, hopeless, helpless, worthless)*
- 0 || Absent.
- 1 || These feeling states indicated only on questioning.
- 2 || These feeling states spontaneously reported verbally.
- 3 || Communicates feeling states non-verbally, i.e. through facial expression, posture, voice and tendency to weep.
- 4 || Patient reports virtually only these feeling states in his/her spontaneous verbal and non-verbal communication.

**2 FEELINGS OF GUILT**
- 0 || Absent.
- 1 || Self reproach, feels he/she has let people down.
- 2 || Ideas of guilt or rumination over past errors or sinful deeds.
- 3 || Present illness is a punishment. Delusions of guilt.
- 4 || Hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations.

**3 SUICIDE**
- 0 || Absent.
- 1 || Feels life is not worth living.
- 2 || Wishes he/she were dead or any thoughts of possible death to self.
- 3 || Ideas or gestures of suicide.
- 4 || Attempts at suicide (any serious attempt rate 4).

**4 INSOMNIA: EARLY IN THE NIGHT**
- 0 || No difficulty falling asleep.
- 1 || Complains of occasional difficulty falling asleep, i.e. more than ½ hour.
- 2 || Complains of nightly difficulty falling asleep.

**5 INSOMNIA: MIDDLE OF THE NIGHT**
- 0 || No difficulty.
- 1 || Patient complains of being restless and disturbed during the night.
- 2 || Waking during the night – any getting out of bed rates 2 (except for purposes of voiding).

**6 INSOMNIA: EARLY HOURS OF THE MORNING**
- 0 || No difficulty.
- 1 || Waking in early hours of the morning but goes back to sleep.
- 2 || Unable to fall asleep again if he/she gets out of bed.

**7 WORK AND ACTIVITIES**
- 0 || No difficulty.
- 1 || Thoughts and feelings of incapacity, fatigue or weakness related to activities, work or hobbies.
- 2 || Loss of interest in activity, hobbies or work – either directly reported by the patient or indirect in listlessness, indecision and vacillation (feels he/she has to push self to work or activities).
- 3 || Decrease in actual time spent in activities or decrease in productivity. Rate 3 if the patient does not spend at least three hours a day in activities (job or hobbies) excluding routine chores.
- 4 || Stopped working because of present illness. Rate 4 if patient engages in no activities except routine chores, or if patient fails to perform routine chores unassisted.

**8 RETARDATION** (slowness of thought and speech, impaired ability to concentrate, decreased motor activity)
- 0 || Normal speech and thought.
- 1 || Slight retardation during the interview.
- 2 || Obvious retardation during the interview.
- 3 || Interview difficult.
- 4 || Complete stupor.

**9 AGITATION**
- 0 || None.
- 1 || Fidgetiness.
- 2 || Playing with hands, hair, etc.
- 3 || Moving about, can't sit still.
- 4 || Hand wringing, nail biting, hair-pulling, biting of lips.

**10 ANXIETY PSYCHIC**
0 || No difficulty.
1 || Subjective tension and irritability.
2 || Worrying about minor matters.
3 || Apprehensive attitude apparent in face or speech.
4 || Fears expressed without questioning.

**11 ANXIETY SOMATIC (physiological concomitants of anxiety) such as:**
gastro-intestinal – dry mouth, wind, indigestion, diarrhea, cramps, belching
cardio-vascular – palpitations, headaches
respiratory – hyperventilation, sighing, urinary frequency, sweating
0 || Absent.
1 || Mild.
2 || Moderate.
3 || Severe.
4 || Incapacitating.

**12 SOMATIC SYMPTOMS GASTRO-INTESTINAL**
0 || None.
1 || Loss of appetite but eating without staff encouragement. Heavy feelings in abdomen.
2 || Difficulty eating without staff urging. Requests or requires laxatives or medication for bowels or medication for gastro-intestinal symptoms.

**13 GENERAL SOMATIC SYMPTOMS**
0 || None.
1 || Heaviness in limbs, back or head. Backaches, headaches, muscle aches. Loss of energy and fatigability.
2 || Any clear-cut symptom rates 2.

**14 GENITAL SYMPTOMS (symptoms such as loss of libido, menstrual disturbances)**
0 || Absent.
1 || Mild.
2 || Severe.

**15 HYPOCHONDRIASIS**
0 || Not present.
1 || Self-absorption (bodily).
2 || Preoccupation with health.
3 || Frequent complaints, requests for help, etc.
4 || Hypochondriacal delusions.

**16 LOSS OF WEIGHT *(RATE EITHER a OR b)***

| | **a) According to the patient:** | **b) According to weekly measurements:** |
|---|---|---|
| 0 | No weight loss. | Less than 1 lb weight loss in week. |
| 1 | Probable weight loss associated with present illness. | Greater than 1 lb weight loss in week. |
| 2 | Definite (according to patient) weight loss. | Greater than 2 lb weight loss in week. |
| 3 | Not assessed. | Not assessed. |

**17 INSIGHT**
0 || Acknowledges being depressed and ill.
1 || Acknowledges illness but attributes cause to bad food, climate, overwork, virus, need for rest, etc.
2 || Denies being ill at all.

Total score: _____

*Source:* Hamilton M. A Rating scale for depression. *Journal of Neurology, Neurosurgery & Psychiatry* 1960; 23: 56–62.

guilt, retardation (as characterized in Figure 13.4), anxiety (psychic type), and general somatic symptoms. Using this subscale, a strong and more convincing level of effect from antidepressant drugs was shown for non-severe depression.

## STOP & CHECK

1. Approximately how many weeks does it take for antidepressant drugs to become effective?
2. Treatment-resistant depression is often identified after multiple failed treatments with antidepressants, including a(n) _____.
3. A particular challenge in antidepressant clinical trials is that patients may improve when taking a(n) _____.

1. at least two to four weeks 2. SSRI 3. placebo

## Pharmacogenetic Factors in Antidepressant Treatment

Pharmacogenetic differences also impact a patient's response to antidepressant drugs, due to pharmacokinetic or pharmacodynamic actions. The activity of liver enzymes for particular drugs varies across patients and alters the circulating levels of drugs (**Table 13.6**). This, in turn, may account for adverse effects some patients experience. For example, polymorphisms of CYP2D6 can account for poor metabolism of antidepressant drugs, causing much higher blood plasma concentrations of the drug than needed for therapeutic effects. The poor metabolism of antidepressant drugs in these cases corresponds to effects seen from taking an unusually high dose of the drug. In a case of a poor-metabolizing patient for CYP2D6 taking the tricylic antidepressant drug nortriptyline, the drug's normal recommended therapeutic dose led to blood plasma concentrations more than double concentrations needed for antidepressant effects. The patient exhibited significant adverse effects of low-pressure dizziness and vertigo—effects normally avoided at the recommended dose (Bertilsson, Dahl, & Tybring, 1997).

Genetic differences also may alter the ability of an antidepressant drug to cross the blood–brain barrier. In a study conducted by Uhr and colleagues (2008), variations in the ABCB1 gene were examined because this gene encodes for P-glycoprotein, a transporter important for the ability of certain antidepressant drugs to cross the

**TABLE 13.6** Selected Pharmacogenetic Factors for Antidepressant Response

| Pharmacogenetic Factor | Function | Impact on Antidepressant Response |
|---|---|---|
| P450 liver enzymes | Affect metabolism of drugs | Cause unexpected blood plasma concentrations, either too high or too low, from a recommended dose for a drug |
| ABCB1 gene polymorphism | Affects P-glycoprotein transporter function in blood–brain barrier | Inhibits passage of certain antidepressant drugs from entering the brain through the blood–brain barrier, reducing antidepressant effects |
| Short variation of serotonin transporter-gene–linked polymorphic region | Affects function of the serotonin membrane transporter; may find fewer serotonin transporters in those with this polymorphism | Reduced antidepressant effects possibly by having fewer transporters to bind to |
| *Val66Met* polymorphism on the gene for BDNF | May reduce BDNF levels and levels of TrkB receptors | Reduced ability of antidepressant drugs to promote neurogenesis |

blood–brain barrier. In patients who had a polymorphism in the ABCB1 gene, full recovery from depression was less likely if they were treated with a drug transported by P-glycoprotein, such as the tricyclic antidepressant drug *amitriptyline (Elavil)*, the SSRIs *paroxetine (Paxil)* and *citalopram (Celexa)*, or the *SNRI venlafaxine (Effexor)* (Table 13.6). They did not find a correlation with the antidepressant drug *mirtazapine (Remeron)*, which does not rely on P-glycoprotein to cross the blood–brain barrier.

Pharmacogenetic factors may also alter serotonin transporter function, an important site of action for many antidepressant drugs. The gene for the serotonin transporter is *SLC6A4*, and it includes a region important for serotonin transporter function called the *serotonin transporter-gene-linked polymorphic region*. Clinicians find a poorer treatment response and shorter time until depressive symptoms return in patients who have a short variation of this region (Horstmann & Binder, 2009; Serretti, Kato, De Ronchi, & Kinoshita, 2007). These effects may be due to a reduced level of serotonin transporters among individuals with this polymorphism, leading to fewer sites for antidepressant drugs to act on (Lesch et al., 1996; Smeraldi et al., 1998).

Finally, genetic expression of neurotrophins may affect antidepressant treatment response. These investigations stem from findings that chronic antidepressant drug administration promotes neurogenesis in the hippocampus. In particular, several studies have focused on the polymorphism called *Val66Met* existing on the gene for BDNF. This polymorphism reduces BDNF levels and may subsequently lead to reduced density of TrkB receptors (Bath et al., 2008; Egan et al., 2003). As noted previously, antidepressant drugs may promote neurogenesis by indirectly activating TrkB receptors. Patients with this polymorphism tend to have poorer treatment response to antidepressant drugs (Horstmann & Binder, 2009; Shimizu, Hashimoto, & Iyo, 2004).

**Review!** Neurotrophins are a family of molecules that promote the survival and plasticity of neurons during development and in adulthood. BDNF binds selectively to TrkB receptors (Chapter 3).

## STOP & CHECK

1. How might a short variation of the serotonin-transporter-gene-linked polymorphic region impact the effectiveness of antidepressant drugs?
2. Two pharmacokinetic factors important for antidepressant drugs that are affected by pharmacogenetic factors are _____.
3. Gene polymorphisms for neurotrophins may diminish the effects of antidepressant drugs on _____.

1. An individual with this polymorphism may have fewer functional serotonin reuptake transporters. Fewer serotonin reuptake transporters mean fewer targets for SSRIs or other antidepressant drugs that block serotonin reuptake. 2. the ability to cross the blood–brain barrier (P-glycoprotein activity) and drug metabolism (CYP2D6 polymorphisms) 3. neurogenesis in the hippocampus

## Combination Drug Strategies for Treating Depression

**Combination drug strategy**
The administration of a medication to adjust the effects of another medication

**Augmentation strategy (or adjunctive treatment/ therapy)**
Administration of a drug intended to boost the therapeutic effects of a medication

**Add-on treatment**
The administration of a medication to adjust the effects of another medication; often used to describe a drug boosting the therapeutic effects of a medication

**Off-label**
A non-government-approved use of a clinically available drug

Recent years have seen an emergence of combination strategies for antidepressant treatments. The purpose of a **combination drug strategy** is to administer a medication to adjust the effects of another medication. We find a number of different terms used to describe these approaches. For drugs intended to boost the therapeutic effects of a medication, we use the term **augmentation strategy** (or **adjunctive treatment or adjunctive therapy**). **Add-on treatments** simply imply an adjustment of a medication's effects by another drug, in this case identical to the term *combination drug strategy* referred to earlier. Yet, most times we find "add-on treatment" regarded as synonymous with "augmentation strategy."

We find the use of *antipsychotic* drugs—drugs developed for treating schizophrenia—as adjunctive treatments (i.e., to strengthen antidepressant effects in this context) for patients who do not respond adequately to antidepressant drugs. Normally, these patients meet the criteria for treatment resistance, as described earlier. Chapter 15 covers antipsychotic drugs in detail, but in general we find that antipsychotic drugs act at dopamine and serotonin receptors, usually as antagonists.

The antipsychotic drugs most commonly used as adjunctive medications, as well as meeting FDA approval for this purpose, are *aripiprazole (Abilify)*, *quetiapine (Seroquel)*, and *olanzapine (Zeprexa)*. We also find *risperidone (Risperdal)* used **off-label** (that is, a non-government-approved use of a clinically available drug) for this purpose. Olanzapine is approved for use only in combination with fluoxetine; in fact, we find a combined olanzapine and fluoxetine pill marketed under the trade name *Symbyax*. These antipsychotic drugs fall under the *atypical* class of antipsychotic drugs, which differ in their therapeutic and adverse effects in some ways compared to many older antipsychotic drugs, termed *typical* antipsychotic drugs (again, more on this in Chapter 15).

In a review of clinical studies that examined the efficacy of atypical antipsychotic drugs as adjunctive treatments for depression, Speilmans and colleagues (2013) found that atypical antipsychotic drugs do provide improvements, albeit modest, in depression symptoms, quality of life, and functional outcomes (e.g., improvements in social and occupational functioning). The study authors also noted that a lack of long-term studies on antipsychotic drugs used adjunctively with antidepressant drugs left them uncertain as to whether potential adverse effects might offset the minimal therapeutic benefits derived from these adjunctive treatment approaches.

We also find drugs used as combination treatments to remedy certain adverse effects brought on by antidepressant medications. A typical example of this is *bupropion (Wellbutrin)* as an add-on medication for treating sexual dysfunction produced by antidepressant drugs, particularly for drugs that inhibit serotonin reuptake (e.g., SSRIs and SNRIs). While used off-label for this purpose, practitioners have for years prescribed bupropion as an add-on therapy to address this particular adverse effect. In reviews of published studies evaluating bupropion for reducing sexual

dysfunction from SSRIs or SNRIs, bupropion appears to reduce sexual dysfunction from a moderate to substantial degree. These improvements mostly occur in women. Among men, medications that treat erectile dysfunction (i.e., impotence), such as *sildenafil (Viagra)* and *tadalafil (Cialis)*, instead appear more effective than bupropion as add-on treatments for treating sexual dysfunction from antidepressant drugs (Taylor et al., 2013). These drugs treat erectile dysfunction by inhibiting phosphodiesterase isozymes that diminish the duration and rigidity of an erection (Boolell et al., 1996; Brock et al., 2002).

## Drug Profile: sildenafil

| | |
|---|---|
| Brand name | *Viagra* |
| Properties | Inhibit phosphodiesterase isozymes |
| Uses | Used for treating erectile dysfunction |
| Similar drugs | Tadalafil (*Cialis*) |

## Combining Psychotherapy and Pharmacotherapy for Treating Depression

The general consensus reached from clinical studies is that a combination of psychotherapy and antidepressant drugs is superior to using antidepressant drugs alone. One of the more common psychotherapies evaluated in combination studies consists of cognitive therapy. Cognitive therapy attempts to adjust one's depressive thoughts (e.g., "I'll never be happy" or "I fail at everything") as a means for improving mood. Combining cognitive therapy with an SSRI, SNRI, or atypical antidepressant drug has been shown to produce greater efficacy for major depressive disorder than using an antidepressant alone or cognitive therapy alone (Hollon et al., 2014; Keller et al., 2000; Thase et al., 1997). Yet, a combination of a tricyclic antidepressant drug with psychotherapy does not appear more effective than psychotherapy alone (Blackburn, Bishop, Glen, Whalley, & Christie, 1981; Hollon et al., 1992).

The benefits derived from a combined approach versus using an antidepressant drug or psychotherapy alone may also depend on the severity of depression. In one study, those with milder depressive symptoms benefited just as well with psychotherapy alone as they did with a combination of psychotherapy with an antidepressant drug. Yet in severe depression, the combination appeared most effective (Thase et al., 1997).

## STOP & CHECK

1. What terms describe a drug used to boost the therapeutic effects of a medication?
2. What type of drug is used to boost the antidepressant effects of an antidepressant drug?
3. Which particular adverse effect might bupropion or a drug like *Viagra* be prescribed as an add-on for an antidepressant drug?
4. Aside from another medication, what might be combined with an antidepressant drug to improve a patient's response to treatment?

1. One of these terms is augmentation *strategy* but we also find the terms *adjunctive treatment* and occasionally *add-on treatment* used as well. 2. antipsychotic drug, nearly always an atypical antipsychotic drug 3. sexual dysfunction 4. psychotherapy, such as cognitive therapy

## Antidepressant Drugs and Monoamine Neurotransmitter Systems

Antidepressant drugs all share direct and indirect effects on monoamine neurotransmission. This has led to investigations to determine the actions most closely linked to reducing depression.

### Antidepressant Drugs and Serotonin Neurotransmission

One of the mechanisms important for producing antidepressant effects concerns enhancing serotonin neurotransmission. We find that most antidepressant drugs increase serotonin levels either through reducing catabolism of serotonin (as with the MAO inhibitors) or by preventing reuptake of serotonin (as with SSRIs, SNRIs, and many tricyclic antidepressant drugs). As a result, greater activation of serotonin receptors occurs. Some antidepressant drugs also directly bind to serotonin receptors, which helps researchers to understand which serotonin receptors may be most important for treating depression.

The serotonin receptor most studied for a role in depression and as a target for treating depression is the 5-$HT_{2C}$ receptor. We find 5-$HT_{2C}$ receptors activated when antidepressant drugs increase serotonin levels. Yet, we also find that many antidepressant drugs directly bind to and serve as *antagonists* for these receptors. Antidepressant drugs serving as antagonists for 5-$HT_{2C}$ receptors include the tricyclic antidepressant drugs imipramine and clomipramine and the SSRI fluoxetine (Millan, 2005; Ni & Miledi, 1997). Further, drugs acting as selective antagonists for 5-$HT_{2C}$ receptors produce antidepressant effects in animal models. Antagonism of 5-$HT_{2C}$ receptors appears to increase dopamine levels in the brain (see following),

which may contribute to antidepressant effects. To account for antidepressant drugs that produce an activation of 5-$HT_{2C}$ receptors (i.e., through increasing serotonin levels), researchers generally agree that chronic treatment with an antidepressant drug will eventually *desensitize* 5-$HT_{2C}$ receptors. The desensitization of 5-$HT_{2C}$ receptors results in a state similar to one achieved by an antagonist acting at these receptors (Martin, Hamon, Lanfumey, & Mongeau, 2014).

The 5-$HT_{1A}$ receptor is another receptor implicated in depression and the actions of antidepressant drugs. In people with major depressive disorder who were never treated with an antidepressant drug, PET imaging studies reveal greater 5-$HT_{1A}$ receptor levels compared to those without depression (Kaufman, DeLorenzo, Choudhury, & Parsey, 2016; Parsey et al., 2006; Parsey et al., 2010). In mice bred to exhibit helplessness as a model of depression, researchers found increased levels of 5-$HT_{1A}$ receptors in structures thought important for depression, including the prefrontal cortex, amygdala, and hippocampus (Naudon, El Yacoubi, Vaugeois, Leroux-Nicollet, & Costentin, 2002). This study further found that chronic administration with an SSRI reduced both depression-like behavior in these mice and 5-$HT_{1A}$ receptor levels. 5-$HT_{1A}$ receptors may also account for depression observed among some individuals treated with the medication *isotretinoin (Accutane)* for acne (Hull & D'Arcy, 2003). A study examining this medication and receptor expression found that isotretinoin increased 5-$HT_{1A}$ receptor levels on cell lines, providing a potential explanation for greater rates of depression among those treated with isotretinoin (Kaufman et al., 2016; O'Reilly, Trent, Bailey, & Lane, 2007).

The black box warning noted earlier for SSRIs concerned a potential increased risk of suicide in teens. This increased risk likely occurs from a potential *reduction* in serotonin during the first days of treatment. After these first days, serotonin should increase as desensitization of receptors that would otherwise inhibit the activity of serotonin neurons occurs. We address the model and precise receptors that may be responsible for diminished serotonin levels in the next chapter (Chapter 14, "From Actions to Effects").

The hypothesis that diminished serotonin levels initially caused by antidepressants may increase risk of suicide coincides with studies examining serotonin metabolite levels in the cerebrospinal fluid of suicide attempters. Researchers consistently find diminished serotonin metabolite levels among depressed patients who attempt suicide compared to depressed patients who do not attempt suicide, irrespective of treatment type (Åsberg, Träskman, & Thorén, 1976; Mann & Malone, 1997; Nordström et al., 1994). Low metabolite levels suggest diminished production of serotonin in the central nervous system.

## Antidepressant Drugs and Dopamine Neurotransmission

Several lines of evidence also suggest that dopamine is critical for antidepressant effects. We begin by noting that acute administration of most antidepressant drugs fails to increase dopamine release or cause other changes in dopamine neurotransmission within the limbic system (Pozzi, Invernizzi, Garavaglia, & Samanin, 1999).

Yet during the course of chronic administration with antidepressant drugs, including the tricyclic antidepressant drugs tianeptine, imipramine, and the SSRI fluoxetine, dopamine levels increase in the nucleus accumbens (D'Aquila, Collu, Gessa, & Serra, 2000). These actions in the nucleus accumbens may treat *anhedonia* (a lack of joy) in depression.

Chronic administration with fluoxetine also increases the availability of dopamine $D_2$ receptors in the limbic system. In a study by Maj, Dziedzicka-Wasylewska, Rogoz, Rogoz, and Skuza (1996), a greater density of limbic system $D_2$ receptors was found in rats chronically treated with fluoxetine compared to rats treated with vehicle (i.e., placebo). In another study, chronic administration with fluoxetine, the tricyclic antidepressant drug desipramine, or the MAO inhibitor tranylcypromine, produced increases in nucleus accumbens levels of mRNA that encode for the synthesis of $D_2$ receptors (Ainsworth, Smith, & Sharp, 1998). Given that increases in dopamine release and dopamine $D_2$ receptors occur in the limbic system after chronic administration, many researchers suspect that these changes, in part, account for the lengthy response time for antidepressant drugs (Skolnick & Basile, 2006).

Elevations in dopamine levels in the prefrontal cortex may occur after acute or chronic administration of an antidepressant drug, depending on the particular drug. For example, Bymaster and colleagues (2002) found that among the SSRI drugs they studied after acute administration, only fluoxetine produced increases in prefrontal cortex dopamine levels as assessed using microdialysis in rats. The researchers noted that fluoxetine was the only drug in their study that served as an antagonist for 5-$HT_{2C}$ receptors. Selective antagonism of 5-$HT_{2C}$ has been shown to increase dopamine concentrations in the frontal cortex, suggesting a potential mechanism for some antidepressant drugs to increase dopamine levels in the prefrontal cortex after acute administration (Gobert et al., 2000). Otherwise, antidepressant drugs increase dopamine levels in the prefrontal cortex after chronic administration (Carlson, Visker, Nielsen, Keller, & Glick, 1996; Tanda, Frau, & Di Chiara, 1996).

## Neuronal Growth Occurs During Antidepressant Treatment

Chronic administration of antidepressant drugs causes neuronal growth and production in the hippocampus (Dranovsky & Hen, 2006; Duman, Malberg, & Thome, 1999; Sahay & Hen, 2007). Because an increase in neuron density occurs over weeks during chronic administration, researchers suspect a link between these changes and the response delay for antidepressant effects (Santarelli et al., 2003). Thus, learning how antidepressant drugs increase proliferation in the hippocampus may aid in developing ways to shorten the response time to these drugs.

The SSRI fluoxetine (*Prozac*) has been shown to increase the activation of TrkB receptors, which are activated by BDNF. In turn, activation of TrkB receptors has been shown to increase the production of neurons in the hippocampus (Li et al., 2008). Together, these findings suggest that SSRIs may produce new cells in the hippocampus via the BDNF system.

Antidepressant-induced neurogenesis in the hippocampus provides a potential insight into what mediates antidepressant drug effects. In general, depression does not appear related to diminished neuronal growth in the hippocampus in humans or in animal models. However, hippocampal neurogenesis appears linked to the hypothalamic-pituitary-adrenal axis and can serve to reduce physiological responses to stress. Promotion of neurogenesis in the hippocampus may also aid in pattern separation of memories, which may aid in recognizing cues for stress and consequently learning to cope with stressors (Eisch & Petrik, 2012).

**Review!** Brain-derived neurotrophic factor (BDNF) is a neurotrophin, which facilitates neurogrowth and neuroconnectivity (Chapter 3).

## STOP & CHECK

1. All current antidepressant drugs increase the levels of one or more _____ neurotransmitters.
2. Chronic administration with an antidepressant drug may increase the number of _____ receptors in the limbic system, possibly accounting for a lengthy response time for antidepressant response.
3. An SSRI such as fluoxetine may increase proliferation by activating _____ receptors for BDNF.

1. monoamine (alternatively, dopamine, norepinephrine, or serotonin) 2. $D_2$ receptors 3. TrkB

## Bipolar Disorder

**Bipolar disorder** is a mental disorder characterized by abnormal changes between depressive and manic mood states, representing two "poles" of mood. Depression in bipolar disorder exhibits the same features of depression characterized earlier in this chapter. **Mania** consists of an abnormal elevation or irritation in mood along with increased arousal or energy levels. Manic behavior may occur as fast speaking, rapidly changing ideas, and impulsive decision making. During a manic episode, individuals may engage in excessive spending, reckless behaviors, drastic decision making, drug abuse, and hypersexuality. We use the term *euthymia* to refer to a stable mood state; in bipolar disorders, we characterize euthymia as expressing neither manic nor depressed symptoms.

**Bipolar disorder**
Mental disorder characterized by abnormal changes between depressive and manic mood states

**Mania**
Consists of an abnormal elevation or irritation in mood along with increased arousal or energy levels

We also find cognitive dysfunction as a feature of bipolar disorder. Martínez-Arán and colleagues (2004) sought to examine cognitive functioning in bipolar disorder by examining participants during a euthymic state and comparing test results to healthy control participants. In these comparisons, those with bipolar disorder

exhibited poorer performance on tests for problem solving and working memory. In other studies, those with bipolar disorder tested during a euthymic state have shown deficits in sustained attention (Bora, Vahip, & Akdeniz, 2006; Clark, Iversen, & Goodwin, 2002). The appearance of cognitive deficits during a euthymic state shows that they are likely inherent to the disorder rather than something shown only during depressive or manic state.

**Type I bipolar disorder**
Type of bipolar disorder that exhibits depression and episodes of severe mania

**Type II bipolar disorder**
Type of bipolar disorder that exhibits depression along with episodes of less-severe mania

The DSM-5 defines two types of bipolar disorder that differ primarily by the severity of mania. **Type I bipolar disorder** consists of exhibiting depression and episodes of severe mania. When presented with a severe manic episode, a mental health professional need not require evidence of depression to make a type I diagnosis. **Type II bipolar disorder** consists of exhibiting depression along with episodes of less-severe mania. We also use the term *hypomania* to refer to this form of mania.

Many patients with bipolar disorder receive an incorrect diagnosis when first presenting to a clinician. According to a study conducted by Hirschfeld, Lewis, and Vornik (2003), nearly 70 percent of individuals with bipolar disorder receive a misdiagnosis, and many of these misdiagnosed patients require seeing an average of four physicians and require more than 10 years to receive a correct diagnosis. Reasons cited for misdiagnosis include gathering limited or incorrect clinical histories from patients and a lack of understanding about bipolar disorder among physicians making the misdiagnosis. The most common incorrect diagnosis is *depression*, which tends to occur most frequently in bipolar disorder. Further, individuals in manic states seldom see a reason to seek help, feeling that nothing is wrong with them. Thus, an individual may be more likely seek help while feeling depressed (Bowden, 2001).

Bipolar disorder is far less prevalent than major depressive disorder. According to a national survey conducted by the National Institute of Mental Health, the lifetime prevalence of any type of bipolar disorder in the United States is 4.4 percent. The average age for the first diagnosis of a bipolar disorder is 20.8 years old (Merikangas et al., 2007).

## Neurobiology of Bipolar Disorder

Neuroimaging studies have revealed that areas of reduced activity in the frontal and temporal lobes of the right hemisphere have a tendency to produce manic episodes, whereas those occurring in the left hemisphere have a tendency to produce depressive episodes. Several studies have shown that the volume of the basal ganglia and thalamus tends to be larger in patients with bipolar disorder.

Diffusion tensor MRI reveals diminished integrity and damage of axons in white matter in the cingulate cortex among those with bipolar disorder. This same imaging method has shown abnormalities in neurons connecting the amygdala to the cingulate cortex and connecting the lateral prefrontal cortex with the orbitofrontal cortex, a structure that closely communicates with the amygdala. Taken together, the altered connections between these structures in bipolar disorder may account for poor regulation of mood (Benedetti et al., 2011).

## STOP & CHECK

1. How do type I and type II bipolar disorders differ?
2. In bipolar disorder, mania is associated with reduced activity in the frontal and temporal lobes, whereas depressive symptoms are associated with reduced activity in the _____.

1. Severe mania is observed in type I bipolar disorder, whereas hypomania occurs in type II bipolar disorder. 2. left hemisphere

## Mood Stabilizers, Anticonvulsants, Antipsychotics, and Antidepressants for Bipolar Disorder

Many of the treatments for bipolar disorder were first developed and approved for the treatment of other mental disorders. Thus, we have few drugs that are considered purely **mood stabilizers**—that is, drugs that reduce both depressive and manic symptoms. Beyond mood stabilizers, other treatments include anticonvulsant drugs and antipsychotic drugs. Although clinicians may also prescribe antidepressant drugs to bipolar disorder patients, they seldom administered antidepressant drugs alone, instead preferring to combine them with another bipolar treatment.

**Mood stabilizer**
Drug that reduces both depressive and manic symptoms

### Lithium

**Lithium** was the first mood stabilizer found effective for bipolar disorder. We find some uses of lithium by early neurologists and psychiatrists, including Silas Weir Mitchell, who referred to using lithium bromide for epilepsy and as a calming agent in 1870, and William Hammond, who administered lithium bromide for acute mania in 1871. Yet, we see references to "bromide" as attributable to the effects of lithium bromide, perhaps more than "lithium" (Cade, 1949; Shorter, 2009). We do find, however, the Danish psychiatrist Frederik Lange using lithium *carbonite* for treating depression in 1894 (Shorter, 2009).

**Lithium**
Mood stabilizer used for treating bipolar disorder

Its effectiveness for mania was later evaluated in 1949 by John Cade, who is most often credited with reintroducing lithium as a medicine for modern psychiatry. Cade served as a physician and superintendent of a hospital in Australia, a position he assumed after spending three years in a Japanese prisoner-of-war camp. After noticing that lithium chloride appeared to calm down guinea pigs, he administered the compound to several manic patients, finding striking reductions in mania. After other investigators validated these findings in Europe and the United States, lithium became a primary treatment for bipolar disorder (Cade, 1949; Shorter, 1997).

## Drug Profile: lithium

| | |
|---|---|
| Brand name | *Camcolit, Eskalith, Lithobid, Lithonate*, among others |
| Properties | Intracellular actions, including second messengers and gene expression; may have neuroprotective effects; may inhibit GSK-3 |
| Uses | Used for treating bipolar disorder; appears more effective for mania than depression |

Since this discovery, hundreds of studies have reported on the mood-stabilizing effects of lithium in bipolar disorder. We can determine the general consensus of lithium's efficacy by reviewing randomized double-blind, placebo-controlled trials conducted in patients with bipolar disorder. Geddes and colleagues (2004) conducted an assessment of five studies that used this design. They found that lithium overall proved consistently more effective than placebo for preventing manic symptoms. However, they failed to see substantial reductions in depressive symptoms. Thus, we find that lithium provides greater efficacy for mania than for depression.

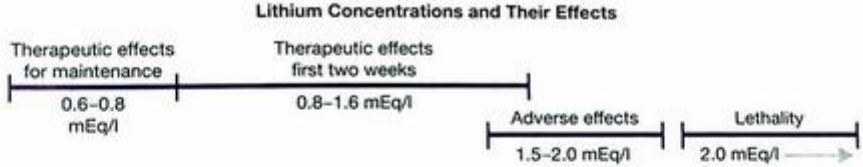
Lithium treatment poses a risk of serious adverse effects. The risk for these adverse effects accompanies a narrow therapeutic index and narrow therapeutic dose range. For these reasons, blood monitoring is used to carefully adjust lithium dosing (**Figure 13.5**). When first beginning lithium therapy, therapeutically effective concentrations fall within a range of 0.8 to 1.2 milliequivalents per liter (mEq/l) of blood. After lithium has accumulated in the body over the course of approximately two weeks, the concentration must be reduced to 0.6 to 0.8 mEq/l to avoid adverse effects. At this stage, these lower concentrations sufficiently maintain therapeutic effects (Ferrier, Tyrer, & Bell, 1995).

**Review!** A therapeutic index represents the difference between lethal and therapeutic drug doses (Chapter 1).

At lithium blood concentrations of 1.5 to 2.0 mEq/l, gastrointestinal effects become prominent, including nausea, vomiting, and diarrhea. Adverse effects may occur at therapeutic blood concentrations as well, including thirst and increased urination, largely because of lithium-induced inhibition of kidney function. Lithium may also produce tremor at therapeutic doses. Higher lithium concentrations, beginning at approximately 2.0 to 2.5 mEq/l, may produce renal failure and muscle rigidity. Moreover, these concentrations pose a serious risk of coma and death. Taken together, even an accidental second ingestion of lithium might increase blood concentrations to near-fatal levels.

**FIGURE 13.5 Therapeutic Dose Window for Lithium**

The dose window for the therapeutic effects of lithium strays near the dose window that produces serious adverse effects. Largely because of this, lithium dosing is adjusted based on levels in blood as expressed as concentration in milliequivalents of blood per liter (mEq/l). The first two weeks of treatment require concentrations near, and possibly overlapping, concentrations noted for serious adverse effects. After the desired therapeutic effects are achieved, lower concentrations of lithium will maintain these effects (noted as "maintenance" in the figure).




### *Lithium's Mechanisms of Action*

Lithium ($Li^+$) is element number 3 on the periodic table and is part of the same grouping as sodium ($Na^+$, atomic number = 11) and potassium ($K^+$, atomic number = 19). As you may recall from Chapter 3, $Na^+$ and $K^+$ play important roles in generating action potentials. Lithium enters neurons through $Na^+$ channels. Once inside a neuron, lithium takes part in a large variety of intracellular actions, including second-messenger actions and gene expression. This presents a great challenge to researchers who are endeavoring to unravel the pharmacological actions important for lithium's mood-stabilizing properties. Based on such studies, the current general consensus among researchers is that lithium's efficacy for bipolar disorder derives from neuroprotective effects against neurodegeneration (Chiu & Chuang, 2010).

We find these neuroprotective effects in preclinical studies. In particular, lithium promotes the survival of neurons during *excitotoxicity*. Lithium also protects neurons during detrimental conditions, including the absence of growth factor, heat shock, and high doses of anticonvulsant drugs. A key action for lithium's neuroprotective effects may involve inhibition of the enzyme *glycogen synthase kinase 3* (Chiu & Chuang, 2010).

**Review!** Excitotoxicity consists of neuronal damage and death caused by overstimulation by glutamate (Chapter 3).

**Glycogen synthase kinase 3 (GSK-3)** is a protein kinase that promotes apoptosis and regulates inflammation. *Apoptosis* is referred to as a programmed cell death, a process important for normal brain development. Excitotoxicity also produces apoptosis. In mice, overexpression of the GSK-3 enzyme causes an increase in behavioral activity, whereas inhibition of the GSK-3 enzyme decreases behavioral activity (O'Brien et al., 2004). These results suggest that GSK-3 inhibition may lead

**Glycogen synthase kinase 3 (GSK-3)**
Protein kinase that promotes apoptosis and regulates inflammation

to decreases in hyperactivity, which is somewhat analogous to mania in humans. In another study, an inhibitor of GSK-3 enzymes led to decreased immobility time in a forced swim test, an indication of antidepressant effects (**Figure 13.6**) (Gould, Einat, Bhat, & Manji, 2004).

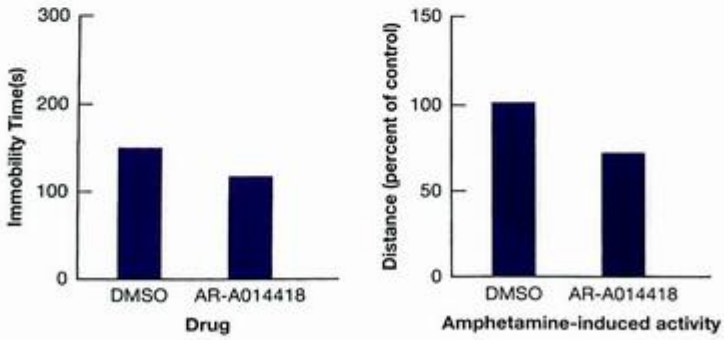
## Anticonvulsant Drugs

Clinicians also use anticonvulsant drugs to treat bipolar disorder, including *carbamazepine (Tegretol)*, *valproic acid* (or *valproate*; trade name is *Depakote*), *oxcarbazepine (Trileptal)*, and *lamotrigine (Lamictal)*. Most anticonvulsant drugs serve as positive modulators for $GABA_A$ receptors, although we find that other $GABA_A$ positive modulators, such as barbiturates, appear ineffective for treating bipolar disorder. Instead, other actions produced by anticonvulsant drugs may account for reduced symptoms in bipolar disorder.

Beyond facilitating GABA neurotransmission, anticonvulsant drugs produce a variety of other effects on neurons. First, many of the anticonvulsant drugs for bipolar disorder inhibit $Na^+$ channel functioning. At therapeutic doses, $Na^+$ channel inhibition largely affects high-frequency action potentials. This action not only likely plays a role in their anti-seizure effects, but also may reduce manic symptoms in bipolar disorder. Second, many of these anticonvulsant drugs inhibit GSK-3 activity,

**FIGURE 13.6 Role of GSK-3 in Lithium's Mood-Stabilizing Effects**

Lithium may reduce depressive and manic symptoms, at least in part, through inhibition of GSK-3, an enzyme that promotes apoptosis and regulates inflammation. A selective inhibitor of GSK-3 activity called *AR-A014418* has been shown to decrease immobility time in rats in a forced swim task, suggesting an antidepressant effect (left figure). In this figure, dimethyl sulfoxide (DMSO) was the vehicle for AR-A014418 and was tested alone to provide a control group. AR-A014418 also reduced hyperactivity induced by amphetamine (right figure).




*Source:* Gould, T. D., Einat, H., Bhat, R., & Manji, H. K. (2004). AR-A014418, a selective GSK-3 inhibitor, produces antidepressant-like effects in the forced swim test. *The International Journal of Neuropsychopharmacology*, 7(4), 387–390. doi:10.1017/S146114, p. 4. Reproduced with permission.

a mechanism of action comparable to the effects of lithium (Chiu & Chuang, 2010; Keck, McElroy, & Nemeroff, 1992).

## Drug Profile: carbamazepine

| | |
|---|---|
| Brand name | *Tegretol* |
| Properties | Positive modulator for $GABA_A$ receptors |
| Uses | Used for treating epileptic seizures; stabilizing mood in bipolar disorder |
| Similar drugs | Valproic acid (*Depakote*), oxcarbazepine (*Trileptal*), and lamotrigine (*Lamictal*) |

## STOP & CHECK

1. Although effective for bipolar disorder, lithium's adverse effects are coupled with a narrow _____ index, requiring careful monitoring of blood concentrations.
2. How does lithium enter neurons?
3. Although lithium has many neurobiological effects, perhaps the most implicated action for treating bipolar disorder is inhibition of the _____ enzyme.

1. therapeutic 2. Lithium enters neurons through sodium channels. 3. GSK-3

### Atypical Antipsychotic Drugs and Antidepressant Drugs

Although clinicians use antipsychotic drugs for the treatment of schizophrenia, antipsychotic drugs are also used for the treatment of bipolar disorder. In particular, the *atypical* antipsychotic drugs have become safer first-line treatments compared to lithium. These drugs include *quetiapine (Seroquel), aripiprazole (Abilify), olanzapine (Zeprexa)*, and *risperidone (Risperdal)*, among others. The compounds serve to reduce and prevent mania from occurring in this disorder (Pae, Serretti, Patkar, & Masand, 2008; Tohen & Zarate, 1997).

A common treatment approach involves a combination of both an atypical antipsychotic drug and an antidepressant drug. One of the first treatment combinations reported for bipolar disorder consisted of the atypical antipsychotic drug olanzapine and the SSRI antidepressant drug fluoxetine (as noted earlier, this combination is now sold as *Symbyax*). During the course of eight weeks, Tohen and colleagues (2003) administered placebo, olanzapine alone, or a treatment combination

of olanzapine and fluoxetine in patients with type I bipolar disorder. They found significantly reduced depression scores after treatment with the drug combination compared to either placebo or olanzapine given alone. Manic symptoms occurred too infrequently in the placebo-treated patients to allow for studying treatment effects on mania in this study.

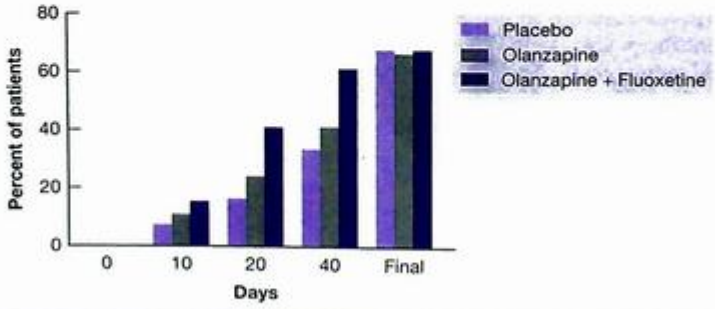
Treatment time course serves as the most clinically important finding in this study. After three weeks of treatment, 50 percent of participants were responsive to the olanzapine and fluoxetine combination compared to only 30 percent of olanzapine-treated patients. Thus, the addition of fluoxetine decreased the amount of time it took for a reduction in depressive symptoms to occur (**Figure 13.7**).

This study provided an important shift in treatment strategies for bipolar disorder. In an extensive review of clinical studies evaluating antipsychotic drugs and other traditional medications for depressive symptoms in bipolar disorder, the fluoxetine–olanzapine combination provided the greatest effects. The atypical antipsychotic drug quetiapine was shown to be the second most effective for depressive symptoms, whereas other antipsychotic drugs and the more traditional treatments for bipolar disorder were inconsistently effective for depressive symptoms (Vieta et al., 2010).

The ability of quetiapine alone to be effective for depressive symptoms is a bit of mystery because, after all, the receptor binding profile for quetiapine is very similar to other atypical antipsychotic drugs, including olanzapine. The unique efficacy quetiapine has for depression may not actually be a result of the quetiapine molecule but of *N-desalkylquetiapine*, an active metabolite of quetiapine. N-desalkylquetiapine chemically resembles a tetracyclic antidepressant drug

**FIGURE 13.7** **Olanzapine and Fluoxetine for the Treatment of Bipolar Disorder**

The figure shows the percentage of patients with bipolar disorder with a substantial improvement in depressive scores during the course of treatment with either placebo, olanzapine alone, or a combination of olanzapine and fluoxetine. More patients in the combination group found improvements in depression sooner compared to the other groups (note the strong placebo effect). *Final* refers to the last assessment, occurring between days 59 and 65 of treatment.




*Source:* Adapted from Tohen et al. (2003).

(like a tricyclic antidepressant, except with four rings), and pharmacological studies reveal that N-desalkylquetiapine inhibits reuptake of serotonin and norepinephrine (Jensen et al., 2008). In this way, quetiapine treatment may functionally serve like a combination of an atypical antipsychotic drug and an antidepressant drug.

## STOP & CHECK

1. Like lithium, anticonvulsant drugs effective for bipolar disorder inhibit the _____ enzyme.
2. Another common bipolar treatment is a combination of an atypical antipsychotic drug and a(n) _____ drug.
3. How might the effects of quetiapine be similar to those produced by a combination of olanzapine and fluoxetine?

1. GSK-3 2. antidepressant drug 3. Quetiapine is an atypical antipsychotic drug, but the active metabolite for quetiapine, N-desalkylquetiapine, may have antidepressant effects.

## From Actions to Effects: Psychedelic Drugs for Treating Depression

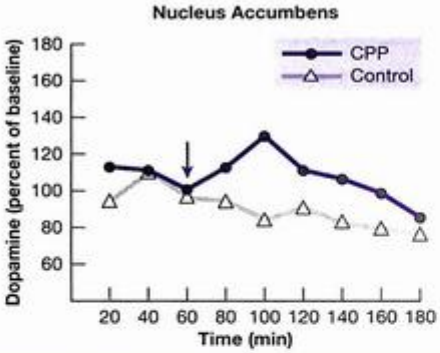
Earlier in the chapter, we discussed esketamine (*Spravato*), a form of ketamine that is the first approved psychedelic antidepressant drug. As a glutamate NMDA receptor antagonist, ketamine acts upon the brain's most excitatory neurotransmitter system and, given this, exhibits widespread effects throughout the brain. A structure that appears important for ketamine's antidepressant effects is the prefrontal cortex. In laboratory rats, ketamine administration increases both dopamine and glutamate concentrations in the prefrontal cortex (Lorrain, Baccei, Bristow, Anderson, & Varney, 2003). Moreover, Li and colleagues (2010) revealed rapid prefrontal cortical synaptic changes, including dendritic spine growth and increased proteins used for intracellular signalling, after acute administration. In particular, ketamine activated a protein kinase called *mammalian target of rapamycin* (mTOR). The effects of ketamine in the prefrontal cortex also may alter dopamine levels in the limbic system, based on the finding that a direct administration of the NMDA receptor antagonist called CPP (an abbreviation of its chemical name[1]) into the prefrontal cortex causes increased dopamine levels in the nucleus accumbens (Del Arco, Segovia, & Mora, 2008) (**Figure 13.8**).

The result of these effects in the prefrontal cortex may alter connectivity to other structures in the brain. Using fMRI, Gärtner and colleagues (2019) assessed depressed patients before and 24 hours after administration of ketamine. In addition,

[1]3-[(R)-2-carboxypiperazin-4-yl]-propyl-1-phophonic acid.

**FIGURE 13.8** **NMDA Receptor Antagonism Increases Nucleus Accumbens Dopamine Concentrations**

In rats, direct administration of the NMDA receptor antagonist CPP into the prefrontal cortex (the downward arrow shows when the injection occurred) caused a significant elevation of dopamine levels in the nucleus accumbens. Dopamine was sampled from the nucleus accumbens using a microdialysis probe. The drug was administered into the prefrontal cortex through a cannula.




*Source:* With kind permission from Springer Science+Business Media: Del Arco, A. (2008). Blockade of NMDA receptors in the prefrontal cortex increases dopamine and acetylcholine release in the nucleus accumbens and motor activity. *Psychopharmacology (Berl), 201*(3), 325–38, fig. 2. doi:10.1007/s00213-008-1288-3.

patients self-reported levels of depression they felt. As demonstrated by other studies, ketamine administration, given as a single intravenous dose, significantly reduced levels of depression. These changes correlated with increased functional connectivity occurring between the prefrontal cortex and the subgenual anterior cingulate cortex. The subgenual anterior cingulate cortex appears overactive in depression and is reduced by treatment with SSRIs.

On the heels of ketamine's breakthrough into depression treatment, several clinical trials show evidence for the hallucinogen psilocybin in depressed patients, including those also suffering from anxiety. The first clinical trial with psilocybin, conducted by Carhart-Harris and colleagues (2016), found that two administrations (seven days apart) of psilocybin to patients with treatment-resistant depression led to reduced depressive symptoms up to three months later. Another study from this group found depressive symptoms reduced up to six months later (Carhart-Harris et al., 2018). In both studies, the second dose given—25 mg—is considered a high dose, which is capable of producing a profound psychedelic experience.

The type of psychedelic experience occurring varies across individuals, with positive episodes most associated with clinical gains (Roseman, Nutt, & Carhart-Harris, 2018). In particular, patients self-report that the psychedelic experiences

most important for their improvement consisted of a reduced feeling of disconnection, which included comments such as being "trapped in their minds," being in a "mental prison," or feeling isolated from others. Patients also self-report that an openness to experiencing unpleasant emotions, rather than avoiding or becoming numb to them, also improved how they felt (Watts, Day, Krzanowski, Nutt, & Carhart-Harris, 2017). According to functional MRI scans conducted 24 hours following psilocybin treatment, patients who experienced improved feelings of depression had reduced activity in the amygdala, which is typically over-activated in depression (Carhart-Harris et al., 2017).

Studies have also evaluated cholinergic muscarinic receptor antagonists as antidepressant drugs. In particular, the drug *scopolamine*, which is known as a psychedelic drug used for recreational purposes (see Chapter 12), has been tested in multiple clinical trials for treating depression. Furey and Drevets (2006) first demonstrated that scopolamine produces a rapid antidepressant effect lasting several days after a single intravenous infusion. A subsequent study found sustained antidepressant effects by administering scopolamine every three to four days to patients with major depressive disorder (Drevets & Furey, 2010). These considerations led Voleti and colleagues (2013) to examine further the potential mechanisms responsible for scopolamine antidepressant effects. They found that scopolamine, like ketamine, stimulates intracellular signalling involving mTOR as well as increasing the number and activity of dendritic spines in the prefrontal cortex. Thus, at present, researchers believe that scopolamine engenders antidepressant effects through a mechanism similar to ketamine. In the history of antidepressant drugs, which were first discovered in the 1950s, psychedelic drugs offer a pharmacological unique approach for reducing depression, and this will continue to be a highly active area of antidepressant research.

## STOP & CHECK

1. In which brain structures have NMDA receptor antagonists, like ketamine, been shown to increase concentrations of dopamine?
2. Beyond ketamine, what hallucinogenic substance has been particularly studied for antidepressant effects?
3. Which intracellular protein appears important for the pharmacological actions for esketamine and potential psychedelic antidepressant drugs?

1. the prefrontal cortex and nucleus accumbens 2. psilocybin 3. *mammalian target of rapamycin* (referred to by the acronym mTOR)

## CHAPTER SUMMARY

A major depressive disorder is characterized by feelings of sadness, worthlessness, and other symptoms that persist for at least two weeks. Persistent depressive disorder consists of fewer symptoms, but these symptoms persist for at least two years. Depression is highly prevalent across age groups and carries a significant risk of suicide.

Neurobiologically, depression appears to be associated with over-activity in the amygdala, reduced activity in the left dorsal prefrontal cortex, and reduced volume of the hippocampus. The classes of antidepressant drugs include MAO inhibitors, tricyclic antidepressant drugs, SSRIs, SNRIs, atypical antidepressant drugs, and psychedelic antidepressant drugs. Important challenges to using antidepressant drugs to treat depression include a lengthy response time, treatment resistance, large placebo effects in clinical trials, the severity of depression, and pharmacogenetic differences.

Bipolar disorder is a mental disorder that is characterized by abnormal changes between depressive and manic mood states. Mania is most severe in type I bipolar disorder and less severe in type II bipolar disorder. Bipolar disorder is associated with a larger basal ganglia and thalamus and disruptions of normal cortical processing. A long-used and still common treatment for bipolar disorder is lithium, which is effective for reducing manic symptoms and, to a lesser extent, depressive symptoms. However, lithium's severe adverse effects coupled with a small therapeutic index makes lithium less desirable if other effective treatments are available. Subsequently, bipolar disorder may be treated with anticonvulsant drugs or antipsychotic drugs. In particular, combined treatment with an antipsychotic drug and an antidepressant drug may be effective for improving depression in bipolar disorder.

## KEY TERMS

Mental disorder 418
Major depressive disorder 418
Persistent depressive disorder (or dysthymia) 419
Vascular depression 422
Monoamine hypothesis of depression 427
MAO inhibitors 427
Irreversible MAO inhibitors 427
Reversible MAO inhibitors 429
Cheese reaction 429
Selective $MAO_B$ inhibitors 429
RIMA drugs (reversible inhibitors of $MAO_A$) 429
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CHAPTER 14

# Treatments for Anxiety Disorders

## Chapter Outline

- Anxiety Disorders
- Structures Involved in Fear and Anxiety
- Anxious Feelings, the Amygdala, and the Sympathetic Nervous System
- Stress and the HPA Axis
- Anxiolytic Drugs for the Treatment of Anxiety
- Antidepressant Drugs for the Treatment of Anxiety Disorders
- MDMA Treatment for Post-traumatic Stress Disorder
- From Actions to Effects: How Do Antidepressant Drugs Reduce Anxiety?

## Learning Objectives

- Describe the symptoms and neurobiology of anxiety
- Compare and contrast the effects of treatments for anxiety
- Explain the pharmacological actions of treatments for anxiety
- Evaluate the use of the psychedelic drug MDMA for treating PTSD

## Anxiety Disorders

We all experience periods of fear and anxiety. We define **fear** as a negative emotion caused by a real or perceived imminent danger or threat. Fear promotes our safety, allowing us to avoid or attempt to handle dangerous situations we may face.

**Fear**
A negative emotion caused by a real or perceived imminent danger or threat

**Anxiety**
Worry and distress concerning potential events or outcomes

Anxiety differs from fear in regard to the likelihood of dangerous situations. We can define **anxiety** as worry and distress concerning potential events or outcomes. Anxiety occurs around events that have yet to happen or that may not even be real. That is, we can think of fear as an emotion occurring in the moment, whereas anxiety is worry about real or perceived events yet to come. Like fear, anxiety too promotes our safety by helping us prepare for such events, potentially limiting their potential for harm or allowing us to avoid the event altogether. Yet, we also find many who become preoccupied with worry or apprehension, to the extent that anxiety disrupts their everyday lives. In these cases, we may define someone as having an *anxiety disorder*.

The *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (DSM-5) considers a number of different types of anxiety disorders. These include separation anxiety disorders (more common in children); selective mutism (also most common in children); specific phobias (e.g., fear of heights, fear of spiders, etc.); panic disorder; agoraphobia; social anxiety disorder; and generalized anxiety disorder (American Psychiatric Association, 2013a). We cover some of these types briefly here.

**Specific phobias**
Significant anxiety provoked by exposure to specific feared objects or situations

**Panic disorder**
Repeat occurrences of panic attacks

**Panic attacks**
An abrupt and possibly unexpected strong physiological reaction accompanied by intense apprehension, fearfulness, or terror

**Agoraphobia**
Anxiety about being in situations from which escape is difficult or embarrassing

**Social anxiety disorder**
Fear of being in or performing in social or public situations

**Generalized anxiety disorder**
Chronic, excessive worry about events, individuals, or activities

**Specific phobias** occur as intense fear or anxiety from a specific object or situation. A *phobia* is something far more severe than a general dislike for something. Instead, a phobia manifests as a strong repulsion to such situations—that is, an arachnophobic (i.e., one who has a fear of spiders) may entirely avoid a room after once encountering a spider there. Depending on the type, a phobia may cause significant disruptions in normal daily living activities.

**Panic disorder** consists of repeat occurrences of **panic attacks**. Panic attacks are an abrupt and possibly unexpected strong physiological reaction accompanied by intense apprehension, fearfulness, or terror. Many individuals mistake their first panic attack as a heart attack, providing us a glimpse into the severity of a panic attack. A panic attack may actually occur in most anxiety disorders, but this is the primary symptom seen in panic disorder.

Another disorder listed in the DSM is **agoraphobia**, defined as a profound fear of being in a situation from which escape is difficult or embarrassing, particularly if a panic attack occurs. **Social anxiety disorder** is a fear of being in or performing in social or public situations. These situations provoke an immediate anxiety response, one that may be severe enough to elicit a panic attack. Although these disorders appear similar, they have important differences. Those with social anxiety disorder fear negative attention from others but can be quite calm when left entirely alone in social situations. Yet, they do fear the negative scrutiny they'll receive if they show anxiety in social situations. Those with agoraphobia avoid these situations out of fear of having a panic attack if they are unable to escape the event or receive any help (American Psychiatric Association, 2013a).

**Generalized anxiety disorder** is characterized by chronic, excessive worry about events, individuals, or activities. Individuals with generalized anxiety disorder may feel worried continually and are subsequently exhausted. This worry often generalizes to various perceived physical ailments, often leading to unnecessary medical care.

Beyond these anxiety disorder types found in the DSM-5, two other disorders that share features of anxiety are obsessive-compulsive disorder and post-traumatic stress disorder. The previous DSM (the DSM-IV Text Revision) included these

disorders as subtypes of anxiety disorder, but the DSM-5 places them in different categories of mental disorders. Because the pharmacological treatments we consider in this chapter have been used to treat obsessive-compulsive disorder and post-traumatic stress disorder, we describe them here and particularly focus on their anxiety features.

**Obsessive–compulsive disorder (OCD)** consists of distress arising from obsessions, with compulsive behavior aimed at reducing distress by addressing the obsessions. Obsessions might consist of thoughts about germs or other contaminations, unresolved doubts (such as whether doors have been left open or home appliances have been left on), and not having objects in a precise order. Thus, common compulsions include excessive hand washing, checking doors or appliances, and organizing objects, respectively. The DSM-5 includes OCD in the category "obsessive-compulsive and related disorders," with related disorders, including *hoarding disorder, body dysmorphic disorder,* and *excoriation (skin-picking) disorder*, among others.

**Obsessive–compulsive disorder (OCD)** Distress arising over obsessions; accompanied by compulsive behavior that endeavors to reduce this distress

The DSM-5 has post-traumatic stress disorder in the category titled "trauma- and stressor-related disorders," which also includes *acute stress disorder, reactive attachment disorders*, and *attachment disorders*, among others. **Post-traumatic stress disorder (PTSD)** is characterized by a persistent state of physiological arousal or exaggerated response to certain stimuli, particularly those associated with a traumatic event. These symptoms appear as great fear, feelings of helplessness, and even horror concerning the causative event. Individuals with PTSD have moments of recall of the traumatic event, possibly occurring in dreams. Some individuals may experience flashbacks in which reality temporarily gives way to reliving the traumatic event (American Psychiatric Association, 2013a). The symptoms of PTSD appear to be long lasting. In a study among Vietnam War veterans conducted 40 years after completion of the war, 8.5 percent of female veterans and 12.2 percent of male veterans were found to have PTSD symptoms related to the war (Marmar et al., 2015).

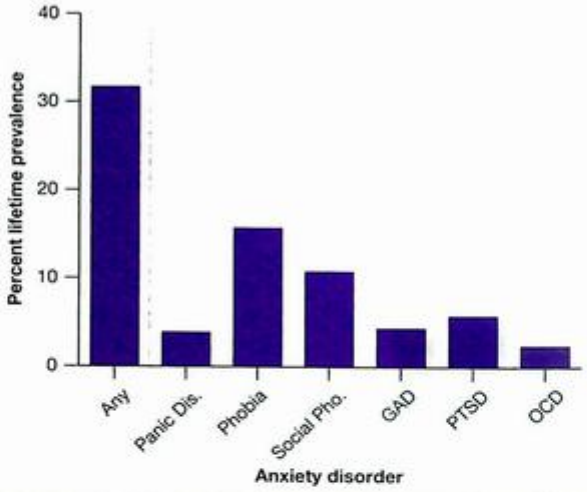
**Post-traumatic stress disorder (PTSD)** Persistent state of physiological arousal or exaggerated response to certain stimuli, particularly those associated with a traumatic event

Anxiety disorders are highly prevalent. The current prevalence rate of any anxiety disorder, including PTSD and OCD, is estimated to be 7.3 percent worldwide. In total, anxiety disorders are twice as common among females as males and appear equally prevalent across different age groups (Baxter, Scott, Vos, & Whiteford, 2013). In an evaluation of lifetime prevalence in the United States, Kessler and colleagues (2012) estimated that 33.7 percent had an anxiety disorder, again including PTSD and OCD (**Figure 14.1**). The majority of these individuals experienced some type of specific phobia or social phobia. A fourth of those experiencing an anxiety disorder reported having PTSD.

Anxiety disorders may develop as a result of both environmental and genetic factors. Childhood physical and sexual abuse correlates highly with having an anxiety disorder in adulthood (Cougle, Timpano, Sachs-Ericsson, Keough, & Riccardi, 2010). Overall, genetic risk accounts for 30 percent to 40 percent of anxiety disorder diagnoses (Norrholm & Ressler, 2009). In particular, genetics accounts for 47 percent of the likelihood of developing PTSD after experiencing a traumatic event (Sartor et al., 2012). Given their prevalence, anxiety disorders have a significant economic burden on society. For example, Olesen and colleagues (2012) estimated that anxiety disorders in Europe cost €74.4 billion (approximately $55.9 billion at the time the study was conducted) per year. Economic cost models for anxiety disorders not only

**FIGURE 14.1 Prevalence of Anxiety Disorders**

Anxiety disorders are among the most prevalent mental disorders. GAD = generalized anxiety disorder. PTSD = post-traumatic stress disorder. OCD = obsessive-compulsive disorder.




*Source:* Data from Kessler et al. (2012).

assess direct psychiatric care but also prescription costs, unnecessary medical care, lost work productivity, and various other factors.

## STOP & CHECK

1. An anxiety about being in situations where escape is difficult or embarrassing is called _____.
2. A profound fear of something such as heights, spiders, or confined spaces is defined as a(n) _____, according to the DSM.

1. agoraphobia 2. specific phobia

## Structures Involved in Fear and Anxiety

As presented in Chapter 2, studies identify the amygdala as a critical structure for fear and anxiety. Increased activity in this structure is associated with fear, anxiety,

and aggression in numerous animal and human studies. In humans, increased activity in the amygdala causes states of fear and anxiety. Dysfunction of the amygdala occurs in every type of anxiety disorder, as well as PTSD (Davis & Whalen, 2001; Shin & Liberzon, 2010). Yet, the amygdala may be less involved in OCD. Rather, researchers associate OCD with abnormal functioning in the thalamus, cingulate cortex, prefrontal cortex, orbitofrontal cortex, basal ganglia, and nucleus accumbens (Graybiel & Rauch, 2000; Laplane et al., 1989).

The amygdala appears responsible for relating stimuli or events to fear and for mediating the physiological and psychological reactions to fear. Studies in both animals and humans consistently reveal increased activity in the amygdala during fear conditioning, a process in which a stimulus is associated with an aversive event such as a shock. Moreover, increases in amygdala activity occur when receiving oral warnings, watching videos of humans being fear conditioned, and seeing pictures of faces with frightened expressions. Researchers find associations between deficient amygdala functioning in humans, which may result from infections, injury, or parasites, with placid reactions to aversive stimuli and self-inflicted injury (Shin & Liberzon, 2010).

The amygdala receives information from many parts of the brain (**Figure 14.2**). The nervous system sends sensory information, including visual, auditory, touch, and pain, from the thalamus to the amygdala via two pathways. First, the thalamo-amygdala pathway sends crude and unprocessed sensory information directly from the thalamus to the amygdala. We refer to this as the *short route* for sensory information from the thalamus. As largely unprocessed information, this pathway provides the amygdala only basic features of a stimulus, such as a loud noise, but does not indicate what the stimulus actually is (Davis & Whalen, 2001).

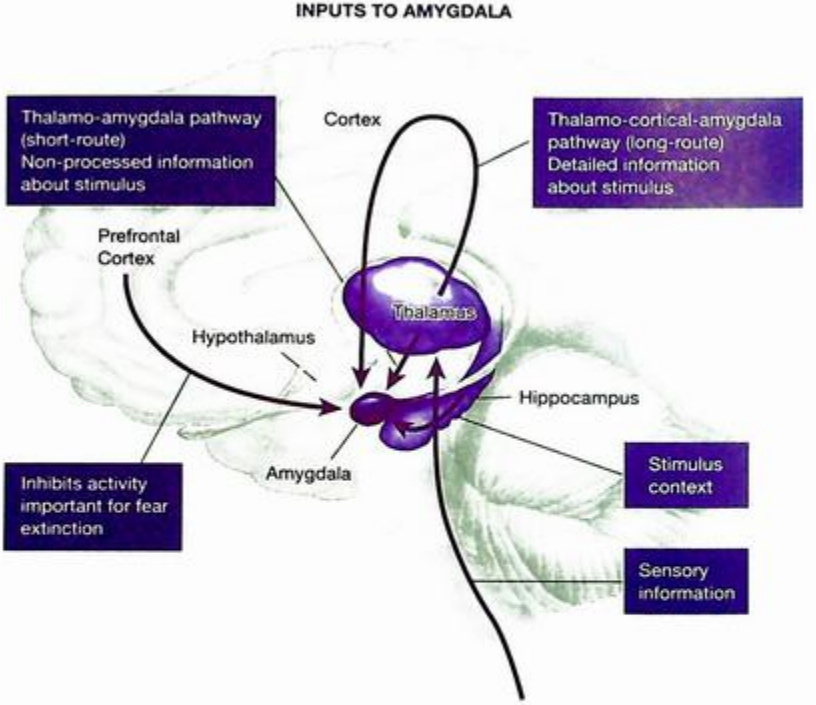
Second, the thalamo-cortical-amygdala pathway sends sensory information to the amygdala after processing in the cerebral cortex. We refer to this as the *long route* for sensory information from the thalamus because it requires a slightly longer amount of time to reach the amygdala. Because the sensory information is processed in the cortex, the information contains information about what the stimulus is. For example, instead of a "loud noise" as the short pathway may communicate, a person may afterward discern a "dog's bark" as the long pathway may communicate (Davis & Whalen, 2001).

The hippocampus sends information on the context surrounding the stimulus to the amygdala. Thus, if the context of the environment is important for the amygdala's response to the stimulus, then information sent from the hippocampus will modify this response. Thus, a person may have a weak fear response when seeing a large dog—the stimulus in this example—behind a large fence—the stimulus context. Inputs to the amygdala from the prefrontal cortex act to reduce amygdala activity, resulting in an inhibited reaction to fearful stimuli. We also find the prefrontal cortex important for extinction of fear conditioning or, in other words, unlearning that particular stimuli are fearful (Davis & Whalen, 2001). We cover the role the amygdala and other structures play in how we experience fear or anxiety in the next section.

An elegant demonstration of the hippocampus's role in pairing a context with fearful stimuli was conducted using optogenetic techniques (see **Box 14.1** for an

**FIGURE 11.2 Sensory Processing for Fear Circuitry**

The amygdala receives sensory inputs from the body and sends information to the prefrontal cortex, hypothalamus, and other areas important for anxiety responses.




overview of optogenetics) by Liu and colleagues (2012). These researchers sought to activate only neurons in the *dentate gyrus* of the hippocampus, a region of the hippocampus particularly important for discriminating between different contexts that were activated when mice underwent a fear-conditioning procedure (see **Box 14.2** for a description of fear conditioning). The objective of this study was to use light to activate channelrhodopsin proteins only on those neurons in the dentate gyrus activated during fear conditioning.

# BOX 14.1

## OPTOGENETICS

*Optogenetics* is a research technique that uses light to alter the firing rate of specific types of neurons (**Box 14.1 Figure 1**). The process relies on ion channels that open when a particular frequency of light (i.e., color) reaches them. Thus, these channels serve as *light-gated* ion channels, in contrast to the voltage-gated ion channels and ligand-gated ion channels referred to in Chapter 3.

**BOX 14.1 FIGURE 1** **Optogenetics**

Researchers use optogenetic techniques to selectively change the activity of one type of neuron (top neuron in this example) by shining light through fiber optic cables onto light-gated ion channels. Neurons lacking light-gated ion channels do have a change in activity when light is shown upon them (bottom neuron).

(Continued)

(Continued)

Optogenetics presently utilizes three different types of ion channels: (1) *channelrhodopsin*, (2) *halorhodopsin*, and (3) *archaerhodopsin* (Zhang et al., 2011). Channelrhodopsin responds best to blue light, which we state specifically as a 480-nanometer wavelength. Positively charged Na+ ions flow through this channel when opened, leading to activation of the neuron. Functionally, these activated channels produce an effect similar to an excitatory postsynaptic potential (EPSP). Thus, the activation of channelrhodopsin by blue light leads a neuron to increase its rate of action potentials (i.e., the firing rate).

Halorhodopsin and archaerhodopsin both produce inhibitory effects when activated. Halorhodopsin responds to green/yellow light (best at 570-nanometer wavelength) and causes the influx of negatively charged $Cl^-$ ions. Archaerhodopsin responds to green light (550- to 576-nanometer wavelength) and causes positively charged $H^+$ ions to leave the neuron (Han et al., 2011; Zhang et al., 2011). In this way, activation of archaerhodopsin produces inhibitory effects on a neuron.

Optogenetics is used in genetically modified organisms (see **Box 2.1** in Chapter 2 for review) to study the nervous system and behavior. Genes that cause the production of light-gated ion channels may be added to an organism's DNA by injecting the organism with an engineered virus. The virus inserts itself into an organism's DNA, where, in this case, the new DNA serves as a gene that will instruct neurons to synthesize these light-gated ion channels.

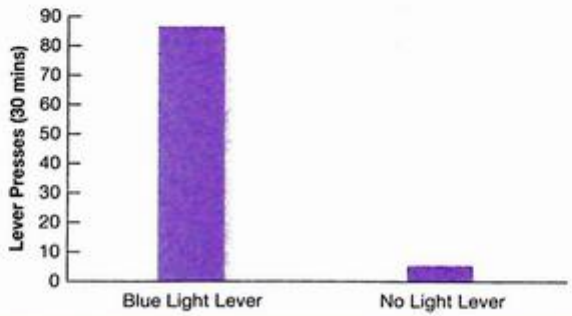
Linking particular neurotransmitter systems to behavior has become one of the main approaches for optogenetics. As noted in **Box 3.1** in Chapter 3, one of the main techniques prior to the invention of optogenetics was the use of electrical stimulation of certain structures in the brain in animals. Yet, no structure in the brain has purely one type of neuron. Even stimulating the ventral tegmental area leads to the activation of more than dopamine neurons.

Yet with optogenetics, researchers can cause only one type of neuron to express light-gated ion channels. To aim at greater selectivity, a researcher may opt to have only dopamine neurons express channelrhodopsin, for example. Doing so would lead blue light, applied by optical fibers implanted in the brain, to selectively activate dopamine neurons.

Steidl and Veverka (2015) performed a behavioral experiment in which optogenetic techniques allowed them to

**BOX 14.1 FIGURE 2** **Optogenetic Self-Stimulation**

Pressing a lever led to either the light-induced activation of laterodorsal tegmental nucleus neurons terminating in the ventral tegmental area (left) or no activation (right). The vertical axis shows the number of lever presses that occurred. We infer from these findings that the rats found the activating lever to produce rewarding effects.




*Source:* Steidl & Veverka (2015).

draw conclusions about the role of a structure called the *laterodorsal tegmental nucleus* in regulating the activity of the ventral tegmental area neurons. They reasoned laterodorsal tegmental nucleus neurons may activate mesolimbic dopamine neurons. If so, greater dopamine release should occur in the nucleus accumbens, the brain's reward center.

To perform this experiment, the researchers injected a virus containing the encoding for channelrhodopsin into the laterodorsal tegmental nucleus in rats. They then emitted a blue light only in the ventral tegmental area, reasoning that axons from the laterodorsal tegmental nucleus should be activated. If this were the case, then behaviors linked to enhanced mesolimbic dopamine activity (e.g., rewarding effects) should occur.

To test this, rats were placed in an operant chamber (i.e., a Skinner box) containing two levers—pressing one lever caused the activation of the blue-light fiber optic cable implanted in the ventral tegmental area, whereas the other did nothing. The result? Rats were willing to work (i.e., press a lever) to activate the blue light, whereas little lever pressing occurred on the inactive lever (**Box 14.1 Figure 2**). The researchers concluded that the blue light caused laterodorsal tegmental nucleus neurons to activate mesolimbic dopamine neurons, which in turn produced rewarding effects.

# BOX 14.2

## ANIMAL MODELS FOR SCREENING ANXIETY TREATMENTS

As with other classes of drugs, *anxiolytics*—drugs that reduce anxiety—are identified in animal behavioral models before they are tested in humans. Many of these models are developed for face validity and thus use tasks that can produce behaviors indicative of stress, fear, or anxiety.

The activity of rodents in an open field provides a simple assessment of anxiety. After being placed in the field, rodents spend much of their time running along the walls or edge of the space rather than the open center. We refer to this as *thigmotaxis*, and it is indicative of fear or anxiety. Drugs effective for anxiety increase the time spent in the center area of the field (Hall, 1934).

The *elevated plus maze* is perhaps the most commonly used model because of its ease, speed, simplicity of equipment, and screening quality (**Box 14.2 Figure 1**). An elevated plus maze has four arms connected in the shape of a plus symbol, and as the name further implies, the maze is elevated above the ground by about three feet. Two of the four arms have tall walls, whereas the other two arms are open. After placing an animal, usually a rat or mouse, in the center of the maze, researchers measure anxiety according to how long the animal spends in the arms with walls compared to the arms without walls. A drug's anxiolytic effects are demonstrated when treated animals spend more time in the arms without walls (Pellow & File, 1986). Although benzodiazepines generally increase the time spent within open arms, SSRIs do not always show this effect (Takeuchi, Owa, Nishino, & Kamei, 2010).

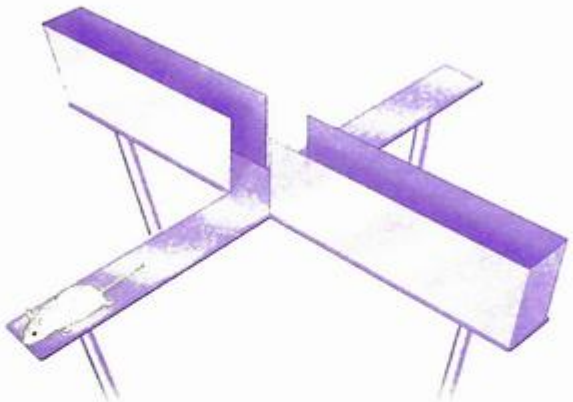
In the *Vogel conflict test*, an animal, usually a rat or mouse, learns to press a lever to earn a lick of water (**Box 14.2 Figure 2a**). At times during this task, a lick will result in a brief, mild electric shock. This presents a conflict: A drink to relieve thirst also causes an aversive shock. The stress or anxiety caused in this task is relieved by anxiolytic drugs—that is, the drugs result in animals taking more licks (Vogel, Beer, & Clody, 1971).

*(Continued)*

(Continued)

**BOX 14.2 FIGURE 1** **Elevated Plus Maze**

An elevated plus maze is a common model for screening anti-anxiety compounds. An elevated plus maze has two closed arms and two open arms. Anxiety is shown when an animal avoids the open arms of the maze.



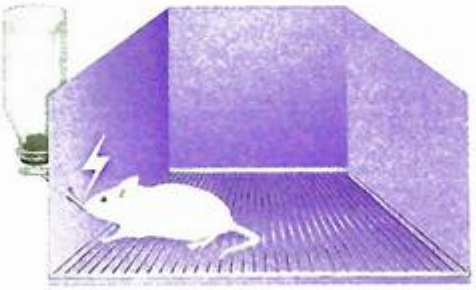
*Fear conditioning* is a process in which animals learn to associate stimuli or an environment with an aversive stimulus (**Box 14.2 Figure 2b**). In a human version of this task, researchers deliver a mild electric shock to a participant's skin while the participant observes a stimulus. During subsequent sessions, the participant demonstrates fear conditioning by startling whenever researchers present the stimulus. Despite the known role of the amygdala in fear conditioning, benzodiazepines seldom inhibit fear responses in this task (Baas et al., 2009; Grillon, 2008).

The *schedule-induced polydipsia paradigm* consists of excessive water consumption occurring during periods between reinforcer delivery for a particular reinforcement schedule (**Box 14.2 Figure 2c**). In a typical experimental design for the schedule-induced polydipsia paradigm, experiments are conducted in animals seeking food pellets in an operant chamber that contains a water bottle. Generally, the food pellets are delivered after set intervals of time, such as every 60 seconds; a sipper tube for a water bottle is always available in the test chamber. Rats are hungry before these sessions but not thirsty. During the intervals between food pellet deliveries, rats tend to drink water from the water bottle. Over time, water consumption in this task develops into excessive drinking, or *polydipsia*. Rats may consume more water during a 30-minute test session than they do throughout an entire day. Schedule-induced polydipsia may be mediated by anxiety, and chronic administration of antidepressant drugs reduces polydipsia.

## BOX 14.2 FIGURE 2 Behavior Models Used for Assessing Anxiety in Animals

(Figure 2a) The Vogel conflict test involves an animal receiving a periodic shock for receiving a lick of water as a reinforcer. (Figure 2b) Fear conditioning involves an organism learning to associate a stimulus with an aversive stimulus, such as electric shock. (Figure 2c) Schedule-induced polydipsia consists of excessive water consumption occurring during periods between reinforcer delivery for a particular reinforcement schedule.

a.



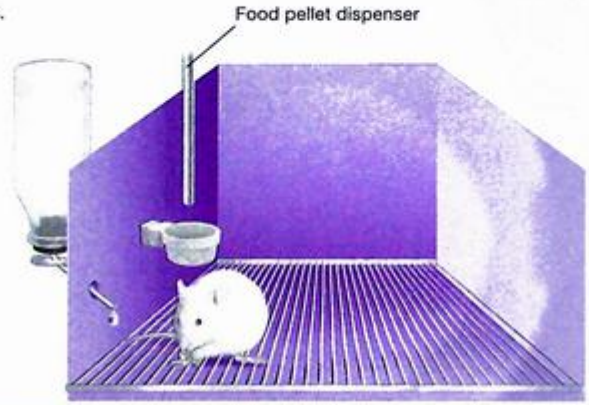
b.

Conditioning involves pairing a stimulus with aversive stimulation

Freezing response does not occur in the same context when the conditioned stimulus is absent

A freezing response can occur in a different context as long as the conditioned stimulus is present

(Continued)




*Source:* Steidl & Veverka (2015).

To select only these neurons presumably active during conditioning of an environmental context with fearful stimuli, Liu and colleagues (2012) used transgenic techniques to cause neurons expressing *c-fos* in the dentate gyrus to also produce channelrhodopsin. We described c-fos as a transcription factor in Chapter 2. C-fos is an *early immediate gene*, a gene rapidly activated in response to stimuli. C-fos, in particular, becomes activated in response to stimuli, making it useful to target in this study.

With all of this set up, Liu and colleagues placed these mice in a chamber and emitted a tone while the mice received intermittent electrical shocks to the chamber's grid floor. In procedures like this, mice quickly learn that the context is associated with aversive stimulation, which depends upon the activation of specific neurons in the dentate gyrus of the hippocampus. Those neurons activated during conditioning triggered c-fos, as neurons activated by stimuli typically do, and they also triggered genetic instructions to begin synthesized channelrhodopsin. Once the conditioning session ended, the researchers also administered the animals a substance to prevent any other activated neurons from synthesizing channelrhodopsin. This last step helped to narrow down expression of channelrhodopsin to only those neurons in the dentate gyrus of the hippocampus that were activated during the conditioning session.

After carrying out these procedures, Liu and colleagues then placed these mice in a different context and watched for freezing responses, a typical fear response in mice. When the optical fiber light was kept off, few freezing responses were observed in this different environment. Thus, none of the environmental stimuli seemed similar enough to those stimuli present during the conditioning session when mice

received the aversive stimulation to cause fear responses. Yet when the optical fiber was turned on, emitting blue light over neurons in the dentate gyrus, mice froze. The researchers found, therefore, a way to trigger the *memory* of contexts associated with fear. The memory, in turn, led mice to emit a fear response.

## STOP & CHECK

1. A key structure mediating fear and anxiety is the _____.
2. Of the two loops for routing sensory information from the thalamus to the amygdala, which is most likely to facilitate fear caused by a sudden, loud noise?

1. amygdala 2. The short loop, which routes crude, unprocessed information from the thalamus directly to the amygdala.

## Anxious Feelings, the Amygdala, and the Sympathetic Nervous System

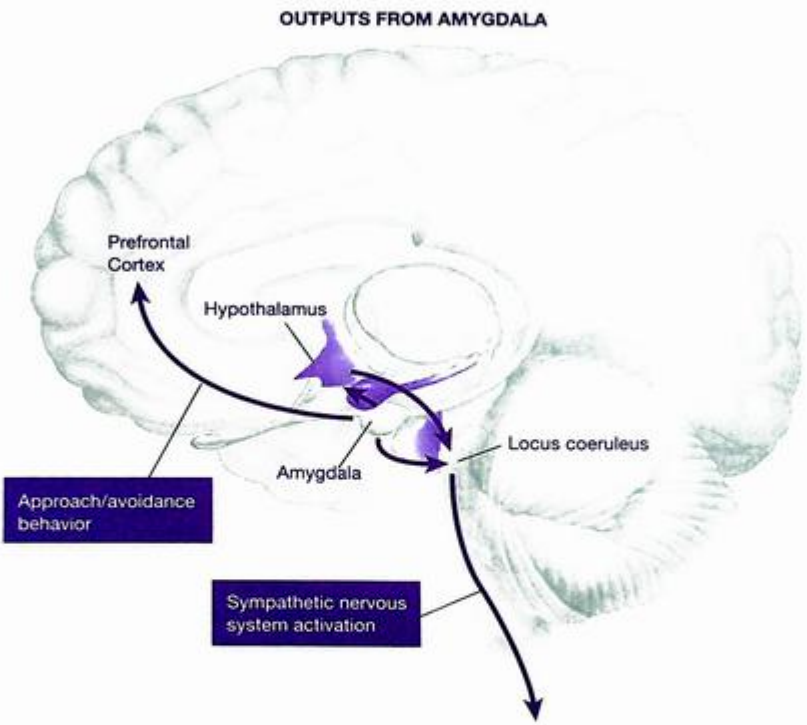
Just as the amygdala receives fear-related stimuli, the amygdala also sends information for fear-related responses (**Figure 14.3**). After receiving fear-related stimulus information, the amygdala sends output signals to the prefrontal cortex, hypothalamus, and locus coeruleus, among other structures. The prefrontal cortex plays a role in determining how we behave in a fearful situation—that is, whether we should approach or avoid a fearful stimulus. The hypothalamus and locus coeruleus facilitate physiological reactions to fear.

The physiological response to fear largely manifests from an activated sympathetic nervous system. Signals from the amygdala and the hypothalamus travel to the locus coeruleus, and the locus coeruleus ultimately causes the release of epinephrine (also referred to as *adrenaline*) and norepinephrine (also referred to as *noradrenaline*) from the adrenal gland. If the sympathetic nervous system is active enough, then respiration, heartbeat, blood pressure, and sweating increase (Davis & Whalen, 2001).

Many anxiety sufferers report having a fear of panic attacks, which consist of strong physiological responses noted by trembling, rapid forceful beating of the heart, restricted breathing, sweating, and dampening of visual or auditory sensations. Objective assessments confirm the physiological effects associated with panic attacks. For example, in a study conducted by Hoehn-Saric and colleagues (2004), individuals with panic disorder or generalized anxiety disorder self-reported anxiety levels at regular intervals throughout the course of several days. These individuals also wore portable physiological recording equipment in an effort to link objective physiological measures with subjective reports of anxiety as they went about their normal daily lives. This study found that physiological measures of increased heart rate and perspiration confirmed self-reports of these events.

**FIGURE 11.3 Fear Circuitry and Behavior**

Outputs from the amygdala go to the prefrontal cortex, hypothalamus, and locus coeruleus. Although the prefrontal cortex is important for approach and avoidance behaviors, the hypothalamus and locus coeruleus are important for sympathetic nervous system activation.




These real-life assessments validate experimentally induced methods of producing panic, including hyperventilation-induced panic and $CO_2$-induced panic. Both methods produce increases in a participant's reported level of panic and physiological responses to panic. Anxiety studies have also reported that individuals with panic disorder appear more sensitive to $CO_2$-induced panic than individuals with other anxiety disorders (Papp et al., 1993; Welkowitz, Papp, Martinez, Browne, & Gorman, 1999). Anxiety medication use or prior cognitive-behavioral therapy reduces $CO_2$-induced panic severity (Gorman, Martinez, Coplan, Kent, & Kleber, 2004).

## Stress and the HPA Axis

We can consider our reactions to short- and long-term stress according to the **general adaptation syndrome** proposed by Selye (1950) (**Table 14.1**). This syndrome has three stages. The first stage is called *alarm* and is characterized by increased physiological arousal in preparation for an emergency situation. The alarm stage consists of the acute reactions to fearful stimuli, including activation of the sympathetic nervous system.

**General adaptation syndrome**
Stress syndrome occurring in three progressive phases: alarm stage, resistance, and exhaustion

The second stage of the general adaptation syndrome is called *resistance* and is characterized by a sustained level of physiological arousal in response to prolonged stress. During this stage, the hypothalamus releases corticotrophin releasing factor, which in turn elicits the release of *adrenocorticotropic hormone (ACTH)* from the pituitary gland. ACTH causes the adrenal gland to release **cortisol**, a stress-related hormone that causes several other effects in the body, including increases in metabolic activity, immune system activity, and glucose and other nutrients. Given their combined distinct role in stress responses, these structures are referred to as the **hypothalamic–pituitary–adrenal (HPA) axis** (**Figure 14.4**).

**Cortisol**
Hormone released from the adrenal gland during stress

**Hypothalamic–pituitary–adrenal (HPA) axis**
A system involved in physiological responses to stress

The third and final stage of the general adaptation syndrome is *exhaustion*. In this stage, the body can no longer maintain the high, sustained levels of physiological arousal that occurred during the second stage. This leads to impaired immune system function and reduced metabolic activity of organs throughout the body. An individual who is in the exhaustion phase is susceptible to disease and feels fatigued.

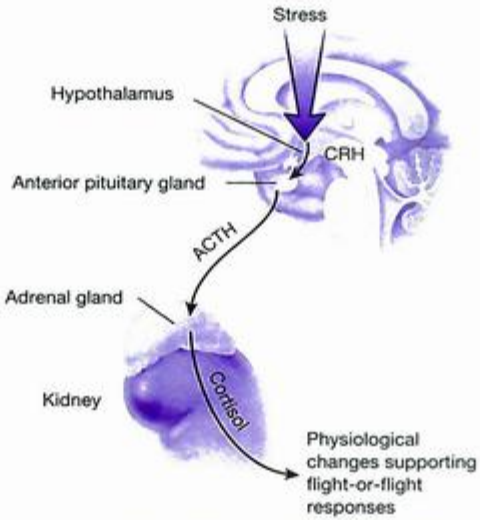
Prolonged increases in cortisol levels are associated with damage to the hippocampus. In this structure, high levels of cortisol are associated with damaged and destroyed neurons, decreased hippocampal size, and memory impairments (Sapolsky, 1992). Further, chronic stress conditions are related to reduced dendrite sizes on neurons and cause memory impairments in rats (Kleen, Sitomer, Killeen, & Conrad, 2006).

**TABLE 14.1 General Adaptation Syndrome**

| Stage | Characteristics | Physiology |
|---|---|---|
| 1: Alarm | Increased physiological arousal to cope with an immediate situation | Hypothalamus activates sympathetic nervous system, including elevated heart rate, breathing, and perspiration |
| 2: Resistance | Sustained level of physiological arousal to cope with unrelenting stressors | Pituitary gland releases ACTH; adrenal gland releases cortisol |
| 3: Exhaustion | Fatigue, susceptibility to disease due to an inability to maintain sustained levels of physiological arousal for unrelenting stressors | Reduced activity of immune system and metabolic activity of organs |

**FIGURE 11.1 The HPA Axis**

The HPA axis includes the hypothalamus, pituitary gland, and adrenal gland. In response to sustained stress, the hypothalamus elicits the anterior pituitary gland to release ACTH (adrenocorticotropic hormone), which in turn causes the adrenal gland to release cortisol.




*Source:* Amanda Tomasikiewicz/Body Scientific Intl.

For these reasons, researchers consider cortisol a *stress hormone* and have heavily studied its potential role in disorders associated with prolonged stress such as PTSD. When referring to changes in hormone or neurochemical levels, researchers often categorize these changes in two phases. A *tonic phase* is generally a baseline state; for PTSD, this might be altered cortisol levels before a traumatic event or altered cortisol levels during a normal day after being diagnosed with PTSD. A *phasic phase* occurs during a stressful event, which for PTSD might have been the actual traumatic event that led to PTSD or the presence of stimuli that might trigger reminders about the traumatic event.

Several studies found consistently lower tonic cortisol levels in individuals with PTSD (Mason, Giller, Kosten, Ostroff, & Podd, 1986; Yehuda et al., 1990). Other studies, however, have shown increased tonic cortisol levels in individuals with PTSD (De Bellis et al., 1999; Pitman & Orr, 1990). Phasic levels of cortisol in PTSD are more consistent across studies. Researchers find high phasic cortisol levels immediately after traumatic events, including military battles and rape (Howard, Olney, Frawley, Peterson, & Guerra, 1955; Resnick, Yehuda, Pitman, & Foy, 1995). Moreover, phasic cortisol levels increase when an individual is exposed to reminders about the traumatic event (Elzinga, Schmahl, Vermetten, van Dyck, & Bremner, 2003).

According to Mouthaan and colleagues (2014), many studies attempting to link PTSD to phasic cortisol levels differ according to how soon after a traumatic event cortisol levels are taken, severity of injury, time of the event, how the samples are taken (e.g., saliva or urine), the number of participants studied, imbalance of male or female participants in a sample, and other methodological factors. To determine whether factors such as these might explain inconsistencies between studies, this group recruited a sample of nearly 400 participants who had blood samples taken within 72 hours of an injury from a traumatic event. The researchers took additional blood samples six weeks and six months later. The large sample size allowed them to have a suitable balance of demographic characteristics among the study participants. They found that low cortisol levels sampled at both six weeks and six months after the traumatic event served to predict the onset of PTSD symptoms. This study provides strong evidence that cortisol levels may actually be diminished in PTSD once other factors are taken into account.

## STOP & CHECK

1. Panic attacks can be experimentally induced through hyperventilation or exposure to _____.
2. During a fear-provoking situation, the approach–avoidance behavior is mediated by the _____.
3. Feelings of fear, such as increased heart rate and faster breathing, result from activation of the _____.
4. The _____ plays an important role in the body's reaction to stress.

1. $CO_2$ gas 2. prefrontal cortex 3. sympathetic nervous system 4. HPA axis

## Anxiolytic Drugs for the Treatment of Anxiety

The term **anxiolytic drug** refers to a drug developed and prescribed for the treatment of anxiety. The first anxiolytic drugs consisted of those of the barbiturate class for the early part of the 20th century, and then later, benzodiazepines. Both classes of drugs exhibit depressant effects and carry a significant risk of abuse. Chapter 8 presented barbiturates and benzodiazepines, including their pharmacological actions and their pharmacological effects.

**Anxiolytic drug** Drug developed and prescribed to treat anxiety

**Review!** Barbiturates and benzodiazepines produce depressant effects through positive modulation of $GABA_A$ receptors (Chapter 3).

### Sedatives for Treating Anxiety

As presented in Chapter 8, *sedatives* refer to compounds that induce calming effects, and we find such substances used throughout human history to help those in anxious

states. Many of the classic sedatives exhibited sleepiness and can thus be considered *sedative-hypnotics* (also presented in Chapter 8). Historically, many remedies for nervousness consisted of concoctions, that included alcohol, opium, cannabinoids (from hemp), or various psychoactive alkaloids.

Other sedatives used around the late 19th and early 20th century included potassium bromide, chloral hydrate, and paraldehyde, all of which have been abandoned due to toxicity, abuse potential, or poorer efficacy compared to modern drugs. Among these compounds, paraldehyde saw the longest use, which ended in the 1970s. We still find paraldehyde used for treating epileptic seizures in children (Ahmad, Ellis, Kamwendo, & Molyneux, 2006).

The 20th century began with the introduction of sedative barbiturate drugs, which became noted for powerful sedative-hypnotic effects. The drugs became popular and were easy to come by. As noted in Chapter 8, accidental and suicidal deaths from barbiturate use rose dramatically around the 1950s. A drug seen as a replacement for barbiturates was meprobamate, better known by its brand name *Miltown*. Meprobamate's popularity came from its ability to engender similar calming effects to barbiturates, but with fewer adverse effects. Users thought meprobamate and related drugs were free from the risk of addiction, based on the drug's product marketing relying on general conceptions of addiction at the time. Yet, reports concerning craving for the substance and physiological withdrawal symptoms alerted practitioners to the risk of liberally prescribing the drug (Essig & Ainslie, 1957; Lemere, 1956). Meprobamate appears to positively modulate $GABA_A$ receptors, although other pharmacological mechanisms of action have yet to be determined (Kumar & Dillon, 2015).

## Drug Profile: meprobamate

| | |
|---|---|
| Brand name | *Miltown* |
| Properties | Positive modulation of $GABA_A$ receptors; other actions unknown |
| Uses | Treatment for anxiety |
| Risks | Addiction to the substance |

Benzodiazepine drugs replaced meprobamate for the treatment of anxiety. Like the barbiturates and meprobamate, benzodiazepines serve as positive modulators for $GABA_A$ receptors. These compounds carry a risk of abuse but are considered safer in this regard compared to barbiturates. Benzodiazepines also lack the significant reductions in respiration found through regular use of barbiturates. Benzodiazepines remain common anxiolytic drugs today and generally are prescribed for use on an "as needed" basis.

## Buspirone for Treating Anxiety

Another drug referred to as an anxiolytic is *buspirone*. Unlike benzodiazepines, buspirone (*BuSpar*) produces anxiolytic effects through partial agonism of serotonin ($5\text{-HT}_{1A}$) receptors. By reducing anxiety through this mechanism, buspirone avoids many of the common adverse effects of benzodiazepines. In particular, buspirone appears to lack abuse potential and it does not strengthen the effects of depressants, such as alcohol or benzodiazepines (DeMartinis, Rynn, Rickels, & Mandos, 2000; van Vliet, den Boer, Westenberg, & Pian, 1997). In this regard, buspirone joins SSRI antidepressants (covered later in this chapter) as a safer treatment option compared to benzodiazepines, particularly in adolescents.

We also find a number of differences in efficacy for treating anxiety compared to benzodiazepines. Unlike benzodiazepines, anxiolytic effects from buspirone do not occur immediately. Rather, buspirone's treatment course more closely resembles antidepressant drugs in that effects may not appear for two to four weeks. Thus, buspirone cannot serve on an "as needed" basis for addressing current anxiety, and in this way, deviates from the general perception of how an anxiolytic drug should act. Thus, buspirone will be unlikely to subdue a current episode of anxiety, but it could reduce frequency of anxiety over time. However, the types of anxiety treated by buspirone also appear far more limiting compared to benzodiazepines. In fact, clinical trials find buspirone effective for reducing symptoms in generalized anxiety disorder but seldom for other types of anxiety disorder (Feighner, Merideth, & Hendrickson, 1982; Lader & Scotto, 1998; Mokhber, Azarpazhooh, Khajehdaluee, Velayati, & Hopwood, 2010).

### Drug Profile: buspirone

| | |
|---|---|
| Brand name | *BuSpar* |
| Properties | Serves as a partial agonist for $5\text{-HT}_{1A}$ receptors |
| Uses | Treatment for generalized anxiety disorder |

Another challenge for using buspirone is extensive first-pass metabolism, which limits the drug's bioavailability. This may mean that for some patients, depending on differences in metabolism, an insufficient concentration of buspirone molecules may reach the brain, precluding any therapeutic effects. CYP-3A4 enzymes in the stomach readily metabolize buspirone, reducing the amount of buspirone for absorption by up to 90 percent (Sakr & Andheria, 2001). This has led to as little as four percent of the drug available for reaching the brain (Gannu et al., 2009). To address this limitation, researchers have developed extended-release tablets, which appear to improve clinical efficacy by providing greater protection of buspirone from stomach enzymes (Sakr & Andheria, 2001). Studies continue to develop improved methods of extended-release tablets for buspirone as well as other delivery methods, such as intranasal administration, to improve the bioavailability of buspirone (Kassem, ElMeshad, & Fares, 2014; Khan, Patil, Yeole, & Gaikwad, 2009).

## Anticonvulsant Drugs for Treating Anxiety

Anticonvulsant drugs, which are used for the treatment of seizures, facilitate the neurotransmission of GABA. As barbiturates and benzodiazepines also facilitate GABAergic neurotransmission, anticonvulsants also appear to exhibit anti-anxiety effects. A variety of anticonvulsants have been found effective for treating anxiety, including valproic acid, carbamazepine, gabapentin, lamotrigine, vigabatrin, and pregabalin. In general, anticonvulsant drugs have shown promising results in case studies and clinical trials for the treatment of anxiety, but we need further studies to determine their safety and efficacy compared to benzodiazepines and antidepressant compounds (Gorman, Kent, & Coplan, 2002).

## Beta Blockers for Coping With Anxiety

**Beta blocker (or beta receptor antagonist)** Drug that inhibits the fight-or-flight response by blocking beta receptors for norepinephrine and epinephrine

Another approach for managing anxiety consists of inhibiting the physiological responses associated with it. A **beta blocker** (or **beta receptor antagonist**) is a drug that inhibits the fight-or-flight response by blocking beta receptors for norepinephrine and epinephrine. The term *blocker* refers to a drug's action as a receptor antagonist. The sympathetic nervous system releases norepinephrine and epinephrine, which activates beta receptors on organs the sympathetic nervous system acts on. During a period of sudden fear, the activation of the sympathetic nervous system causes the activation of beta receptors, thereby rapidly increasing heart rate, breathing, and perspiration.

The FDA approved beta blockers for cardiovascular conditions, such as congestive heart failure and hypertension, but they are prescribed off-label for anxiety. Examples of beta blockers include propranolol, acebutolol, and bisoprolol, among many others. For anxiety, beta blockers do not treat the emotions of anxiety, as would be found with a benzodiazepine, but instead, inhibit the physiological response to anxiety. Also unlike benzodiazepines, beta blockers do not impair cognitive performance. Thus, beta blockers may help a person to get through an anxiety-provoking situation, but one in which the person must rely on cognitive performance. For example, a beta blocker may aid an individual with a fear of public speaking to overcome a strong physiological fear response while keeping one's intellectual capacity intact (Dooley, 2015).

### Drug Profile: propranolol

| | |
|---|---|
| Brand name | *Inderal* |
| Properties | Antagonist for norepinephrine and epinephrine beta receptors; inhibits sympathetic nervous system fight-or-flight responses |
| Uses | For anxiety, inhibits fight-or-flight response during an anxiety-provoking situation |
| Similar compounds | Acebutolol (*Sectral*) and bisoprolol (*Zebeta*) |

## STOP & CHECK

1. For social anxiety disorder, why might a physician prescribe a benzodiazepine drug instead of buspirone?
2. Why might anticonvulsant drugs effectively treat anxiety?

1. A benzodiazepine produces acute sedative effects across types of anxiety, whereas buspirone produces effects from chronic administration and appears effective only for generalized anxiety disorder. 2. Anticonvulsant drugs such as benzodiazepines and barbiturates facilitate the activation of $GABA_A$ receptors.

## Antidepressant Drugs for the Treatment of Anxiety Disorders

Although this chapter has so far focused on the anxiolytic drugs barbiturates and benzodiazepines, the first-line treatments for anxiety disorders have shifted from these medications to antidepressant drugs. Among the antidepressant drugs, we find the selective serotonin reuptake inhibitors (SSRIs) and the serotonin–norepinephrine reuptake inhibitors (SNRIs) most used for treating anxiety.

SSRIs and SNRIs have become the first-line treatments for anxiety disorders. As described in Chapter 13, SSRIs and SNRIs both prevent the reuptake of serotonin through serotonin membrane transporters, and SNRIs also prevent the reuptake of norepinephrine through norepinephrine membrane transporters. Serotonin membrane transporters are of particular interest in anxiety disorders, based on genetic studies linking serotonin transporter gene polymorphisms to anxiety. In particular, individuals found to have a short allele, expressed homozygously or even heterozygously, in the serotonin transporter gene are more likely to exhibit anxiety as a personality trait (Lesch et al., 1996; Sen, Burmeister, & Ghosh, 2004). Those with the short allele of the serotonin transporter also exhibit greater activity in the amygdala based on fMRI studies (Hariri et al., 2002).

The SSRIs *paroxetine (Paxil)* and *fluoxetine (Prozac)* have both demonstrated an efficacy in clinical trials for panic disorder, social phobia, generalized anxiety disorder, and post-traumatic stress disorder (Gorman et al., 2002). Moreover, researchers have found paroxetine effective versus placebo for the treatment of specific phobias (Benjamin, Ben-Zion, Karbofsky, & Dannon, 2000). Clinical studies also find SNRIs effective for anxiety disorders. *Duloxetine (Cymbalta)* met approval by the Food and Drug Administration (FDA) in 2008 for the treatment of general anxiety, based on a series of positive clinical studies (Carter & McCormack, 2009). *Venlafaxine (Effexor)* also has proven effective and has been approved by the FDA for generalized anxiety disorder and social phobia (Altamura, Pioli, Vitto, & Mannu, 1999; Davidson, DuPont, Hedges, & Haskins, 1999). As in the treatment of depression, SSRIs and SNRIs require at least two weeks to relieve the symptoms of anxiety.

Clinical studies generally find SSRIs and SNRIs effective for the treatment of OCD, but the response time appears longer than for other anxiety disorders, often ranging up to 10–12 weeks. The SSRI *fluvoxamine (Luvox)* has long been considered the first-line treatment of OCD as well as impulse control disorders, eating disorders, and Tourette's syndrome (Goodman, Ward, Kablinger, & Murphy, 1997). Antipsychotic drugs may also augment the effects of SSRIs for treating OCD. Diniz and colleagues (2010) found that the atypical antipsychotic drug *quetiapine (Seroquel)* improved the response to an SSRI in OCD patients who failed to respond to SSRI treatment alone.

Although SSRIs and SNRIs have become the first-line treatments for anxiety, approximately one-third of patients do not respond adequately. This failure rate is found in depression as well. **Table 14.2** compares antidepressant drugs to benzodiazepines for the treatment of anxiety.

## STOP & CHECK

1. Antidepressant drugs such as SSRIs and SNRIs have become first-line treatments for _____.
2. Unlike the response time for other anxiety disorders, the response time for _____ often ranges from 10 to 12 weeks.

1. anxiety disorders 2. OCD

**TABLE 14.2** SSRIs/SNRIs Versus Benzodiazepines for the Treatment of Anxiety

| | SSRI/SNRI | Benzodiazepine |
|---|---|---|
| Risk of addiction | Unlikely | Possible, especially in moderate drinkers or those with a history of illicit substance use |
| Physical withdrawal symptoms | Serotonin discontinuation syndrome when withdrawal is abrupt | Physiological withdrawal symptoms with abrupt discontinuation |
| Efficacy | Effective for all types of anxiety; approximately one-third of patients are unresponsive | Most patients responsive to sedative effects; not effective for OCD |
| Response time | Two to four weeks (8–10 weeks for OCD) | Immediate |

## MDMA Treatment for Post-Traumatic Stress Disorder

Psychedelic drugs have not only been evaluated for the treatment of depression, as reviewed in Chapter 13, but some psychedelic drugs have been evaluated for the treatment of PTSD. The psychedelic drug receiving the most attention for PTSD is MDMA. Due to an accumulation of positive findings from small sample size studies, the FDA granted *Breakthrough Therapy Designation* status in 2017 to MDMA to allow U.S. clinical studies for the treatment of PTSD. All clinical studies for PTSD with MDMA include psychotherapy, and therefore, the term used for this treatment approach is *MDMA-assisted psychotherapy.* Most of the funding for U.S. clinical trials for this approach has come from the non-profit organization *Multidisciplinary Association for Psychedelic Studies.* Although approved for clinical studies, MDMA remains a schedule I controlled substance.

The general approach for MDMA-assisted psychotherapy consists of having a patient lie down on a sofa or bed immediately after taking MDMA. The patient is made comfortable and asked to wear a blindfold. Sitting next to the sofa, the therapist holds the patient's hand and engages in psychotherapy, particularly regarding events associated with sources of distress (**Figure 14.5**). Clinicians who study MDMA's empathogenic effects find that MDMA may reduce resistance to thinking about an event or facilitate emotions surrounding the effect. In psychotherapy, reducing such barriers provides a therapist access to the root psychic causes of a psychological disorder (Parrott, 2014).

**FIGURE 14.5** **MDMA-Assisted Psychotherapy**

A psychotherapist talks to a patient experiencing the effects of MDMA as an aid for psychotherapy for the treatment of PTSD.

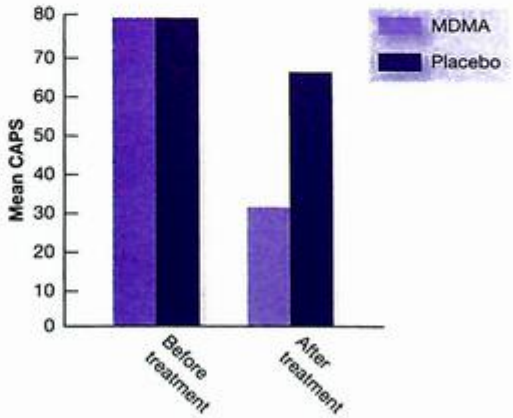
Courtesy of the Multidisciplinary Association for Psychedelic Studies, licensed under CC BY-SA 4.0

The first clinical study on MDMA was reported in 2008 and conducted in Spain. Bouso and colleagues (2008) administered four women with PTSD a single low dose of MDMA, followed by six hours of psychotherapy. Two women with PTSD in the study received placebo. A post-treatment assessment found improvements in three out of four women treated with MDMA, compared to the two women treated with placebo. The study had intended to include more participants as well as more assessments, but political and media pressure led to an abrupt halt to the study, leaving them with only six study participants who had completed at least a portion of the study.

The first complete clinical trial with MDMA was reported in 2011. In this study, Mithoefer and colleagues (2011) assessed low-dose MDMA treatment in conjunction with psychotherapy in patients with PTSD. During the course of the study, patients received either one or two treatments with MDMA or a placebo. Overall, MDMA-treated patients exhibited an 83 percent reduction in PTSD symptoms, whereas placebo-treated PTSD patients exhibited only a 25 percent reduction in PTSD symptoms (**Figure 14.6**). The MDMA doses used produced few physiological or adverse effects. A follow-up of these same study participants 17 to 74 months after the completion of the study revealed all but two participants maintained clinical improvements in PTSD (Mithoefer et al., 2013).

**FIGURE 14.6** **Effects of MDMA With Psychotherapy on Symptoms of PTSD**

MDMA treatment reduced PTSD symptoms according to scores on the Clinician-Administered PTSD Scale (CAPS) to a greater extent than placebo treatment.




*Source:* Adapted from Michael C Mithoefer, Mark T Wagner, Ann T Mithoefer, Lisa Jerome, and Rick Doblin. The safety and efficacy of ±3,4-methylenedioxymethamphetamine-assisted psychotherapy in subjects with chronic, treatment-resistant posttraumatic stress disorder: the first randomized controlled pilot study. *J Psychopharmacol*, April 2011 25: 439–452, first published on July 19, 2010. doi: 10.1177/0269881110378371, p. 13.

In a later study that used MDMA for treating PTSD, Oehen and colleagues (2013) found that patients self-reported improvements in PTSD, but that improvements were not seen on the same measure used by the study shown in Figure 12.11. These researchers did agree with this early report that MDMA appeared safe to use when administered by medical practitioners and again for a limited number of treatments. In a study conducted by Mithoefer and colleagues (2018), two treatments with MDMA, separated by three to five weeks, among first-responders with PTSD led to reduced PTSD symptoms according to multiple indices. One of these measures also found *post-traumatic growth*—a sense of growing from the traumatic event. Those who experience post-traumatic growth exhibit a feeling of greater personal strength, appreciation for life, investment in relationships, and positive spiritual change.

Thus, the apparent success of MDMA-assisted psychotherapy for PTSD in these first clinical studies supports previous anecdotal claims from therapists who employed MDMA during the years before the DEA's schedule I categorization. However, clinical study researchers today benefit from knowledge of MDMA's neurotoxic effects and seem to have chosen lower doses in response to this evidence. Still, other reports caution on the use of MDMA as a pharmacotherapy, citing resemblances to the effects of MDMA with LSD, potential negative subjective effects occurring from MDMA, rebound effects that occur, and the risk of neurotoxicity.

Researchers cite two primary pharmacological actions and effects that might facilitate MDMA's therapeutic effects for aiding psychotherapy. MDMA enhances the release of the neurohormone oxytocin, which may aid in the sense of understanding and interpreting one's emotions. MDMA also reduces activity in the amygdala, which may dampen one's feelings of fear. Taken together, MDMA may enhance psychotherapy for PTSD patients by allowing them to engage with their emotions concerning their traumatic event without experiencing high levels of stress that normally prevent them from doing so (Johansen & Krebs, 2009).

**Review!** Oxytocin facilitates a sense of closeness with others, trust, and interpreting of emotions (Chapter 3).

## STOP & CHECK

1. What do all treatment approaches for PTSD using MDMA include?
2. How might the hormone oxytocin contribute to MDMA's therapeutic effects?

1. psychotherapy 2. Oxytocin may aid in the sense of understanding and interpreting one's emotions, which coincides with the efforts of psychotherapy.

## From Actions to Effects: How Do Antidepressant Drugs Reduce Anxiety?

As presented in Chapter 13, a key pharmacological action of most antidepressant drugs consists of increased concentrations of serotonin. These concentrations increase during chronic administration of antidepressant drugs. Given that a delayed response to antidepressant drugs occurs for both the treatment of depression and the treatment of anxiety, researchers have focused on potential mechanisms that may lead to greater increases in serotonin concentrations over the course of chronic administration. These mechanisms include serotonin transporters, 5-$HT_{1A}$ receptors, and $\alpha_2$ heteroceptors as shown in **Figure 14.7**.

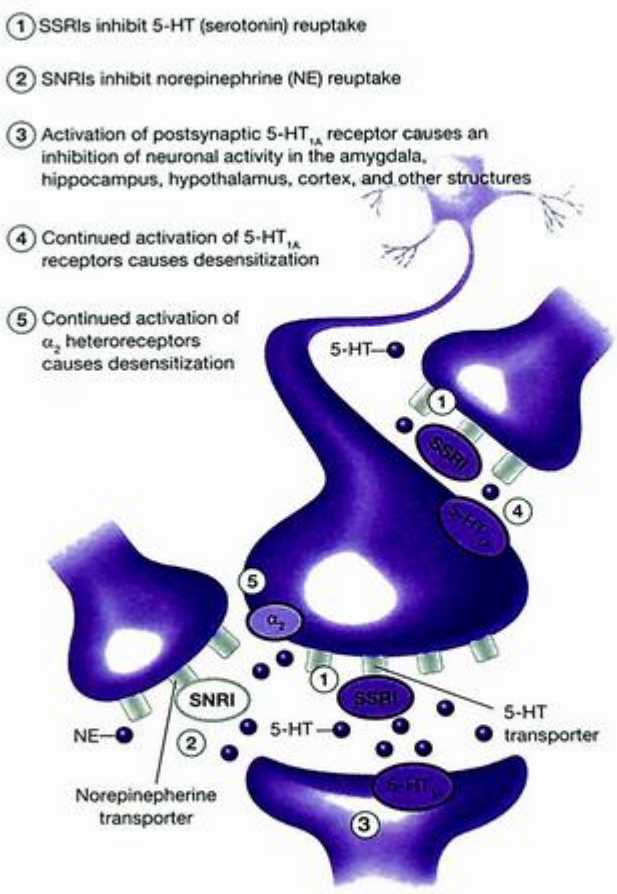
Figure 14.7 labels these processes occurring in an arrangement of serotonin and norepinephrine neurons. First, we find that an SSRI (as well as an SNRI) blocks serotonin membrane transporters, preventing reuptake of serotonin and therefore increasing levels of serotonin outside of the neuron. Yet, these increases must be too low to achieve anxiolytic and antidepressant effects if a drug is only given acutely. Second, we note an SNRI will also inhibit reuptake of norepinephrine through norepinephrine membrane transporters. We can find some norepinephrine axon terminals near serotonin synapses; in this way, released norepinephrine can bind to $\alpha_2$ heteroceptors located on serotonin axon terminals.

Third, evidence suggests that postsynaptic 5-$HT_{1A}$ receptors serve a critical function for serotonin's effects on anxiety. We find postsynaptic 5-$HT_{1A}$ receptors in the cerebral cortex, hippocampus, hypothalamus, and amygdala (Aznar, Qian, Shah, Rahbek, & Knudsen, 2003). 5-$HT_{1A}$ receptor knock-out mice exhibit greater levels of anxiety compared to normal mice (Gross, Santarelli, Brunner, Zhuang, & Hen, 2000; Olivier et al., 2001). In rats, direct injection of the 5-$HT_{1A}$ receptor partial agonist 8-OH-DPAT into the amygdala decreases anxiety in an *elevated plus maze* (Zangrossi, Viana, & Graeff, 1999). Box 14.2 describes the elevated plus maze procedure and other models used for screening treatments for anxiety. Prolonged activation of postsynaptic 5-$HT_{1A}$ receptors causes *sensitization* of these receptors. Sensitized postsynaptic 5-$HT_{1A}$ receptors may enhance serotonin's inhibitory effects on those neurons and ultimately reduce activity in those structures, thereby producing anxiolytic effects. Activation of inhibitory postsynaptic 5-$HT_{2A}$ receptors in these structures may serve a similar role.

Fourth, to understand why serotonin levels may not be high enough to achieve therapeutic effects, we can look to both presynaptic 5-$HT_{1A}$ receptors and $\alpha_2$ heteroceptors. We find 5-$HT_{1A}$ receptors located presynaptically on serotonin neurons and acting as autoreceptors, serving to inhibit serotonin release from the neuron. Rather than finding these receptors at the axon terminal, we instead find them on the somas and dendrites of serotonin neurons. Thus, we refer to these types of receptors as *somatodendritic autoreceptors*. During acute administration, increased serotonin concentrations activate somatodendritic 5-$HT_{1A}$ receptors, causing inhibition of serotonin neurons these receptors are found on. Not only does this diminish the ability of SSRIs (and SNRIs) to increase serotonin concentrations from those particular neurons, but for some individuals, initial treatment with an SSRI may actually *lower* serotonin levels.

**FIGURE 14.7** **Interaction of Norepinephrine and Serotonin Receptors in Antidepressant Drug Effects for Anxiety**

SSRIs and SNRIs produce desensitization at presynaptic 5-$HT_{1A}$ autoreceptors on serotonin (5-HT) neurons, and SNRIs also produce desensitization of presynaptic $\alpha_2$ adrenoceptors (acting as heteroceptors) on serotonin axon terminals. Desensitization, in turn, enhances the release of 5-HT, possibly accounting for the effects of SSRIs and SNRIs on anxiety.



If greater serotonin concentrations are associated with reduced depression, then lower serotonin concentrations should *increase* depression. This may explain why some individuals treated with antidepressants for depression become *more* depressed during the early days of treatment. As noted in Chapter 13, a small percentage of adolescents may become suicidal when first beginning treatment with an antidepressant drug. 5-$HT_{1A}$ receptor levels, in particular, have been investigated using PET imaging among those with major depressive disorder who attempted suicide compared to those who did not. 5-$HT_{1A}$ receptors were higher in brain stem raphe nuclei, a structure where somatodendritic 5-$HT_{1A}$ receptors are found among suicide attempters compared to non-suicide attempters (Sullivan et al., 2015). Connecting these findings with the actions of the somatodendritic 5-$HT_{1A}$ receptors described earlier, greater somatodendritic 5-$HT_{1A}$ receptor levels may increase the inhibition of serotonin neurons and lead to lower serotonin levels. In fact, researchers also find lower serotonin metabolite levels in cerebrospinal fluid, an indication of lower serotonin production, among suicide attempters, as noted in Chapter 13.

Continuing the fourth point, chronic administration of an SSRI (or SNRI) may eventually cause desensitization of somatodendritic 5-$HT_{1A}$ receptors due to reduced G protein activity (Hensler, 2002). Desensitized 5-$HT_{1A}$ autoreceptors provide less inhibition of serotonin neurons, thereby increasing the activity of serotonin neurons and the release of serotonin (Blier & Abbott, 2001). Contributing to these effects is a downregulation of serotonin membrane transporters also resulting from chronic administration (Benmansour et al., 1999). Downregulation of serotonin membrane transporters leads to fewer transporters available for reuptake of serotonin.

Fifth, we also find a desensitization of $\alpha_2$ heteroceptors occurring over the course of chronic administration (Mongeau, de Montigny, & Blier, 1994). As these receptors are inhibitory, their desensitization provides less inhibition of serotonin release from serotonin neurons.

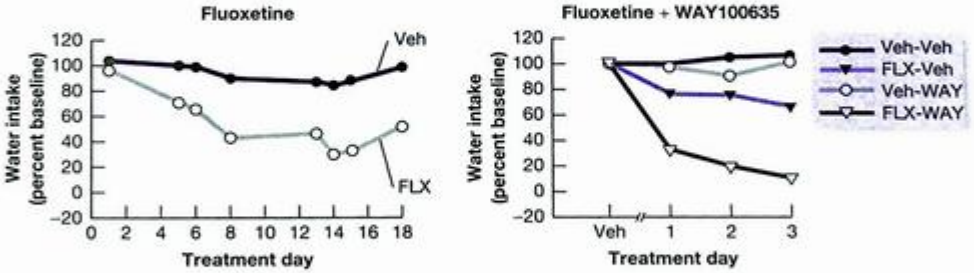
**Review!** A heteroceptor is a presynaptic receptor that is activated by neurotransmitters different from those released from the axon terminal (Chapter 3).

Given all this, pharmacologically enhancing serotonin levels may shorten the response time for antidepressant drugs for the treatment of anxiety as well as depression. For example, Hogg and Dalvi (2004) used the schedule-induced polydipsia paradigm (a model used for screening anxiolytic drugs) to evaluate the effects of repeated administration with the SSRI fluoxetine to reduce water intake over the course of 6 days of administration in rats (**Figure 14.8**). Adding the 5-$HT_{1A}$ receptor antagonist WAY100635 (WAY) with fluoxetine treatment significantly reduced the number of days it took for water intake to be reduced (an anxiolytic effect). In fact, this reduction was shown on the first day of drug treatment.

We find a similar result reported by Prus and colleagues (2015), who tested an $\alpha_2$ adrenoceptor antagonist using the schedule-induced polydipsia paradigm. In this study, the $\alpha_2$ adrenoceptor antagonist yohimbine increased the suppression of drinking produced by fluoxetine. The researchers concluded that antagonism of

**FIGURE 11.8** **A 5-HT$_{1A}$ Receptor Antagonist Shortened the Response Time for the SSRI Fluoxetine in the Schedule-Induced Polydipsia Model**

Fluoxetine (FLX, left) reduces water intake after six days of administration in rats using a schedule-induced polydipsia paradigm. The administration of the 5-HT$_{1A}$ receptor antagonist WAY100635 (WAY) with fluoxetine significantly reduced the number of days it took for water intake to be reduced. In fact, this reduction was shown on the first day of drug treatment. Veh = vehicle (i.e., the drug's solvent without the drug).




*Source:* Hogg and Dalvi (2004). Reprinted with permission.

$\alpha_2$ adrenoceptors may have prevented inhibition of serotonin release, thereby causing an increase in serotonin levels. In human patients with major depressive disorder, treatment with yohimbine also has shortened the time needed for antidepressant effects to occur (Sanacora et al., 2004).

Fifth, postsynaptic receptors for norepinephrine may also contribute to reductions in anxiety. Norepinephrine neurons from the locus coeruleus elicit sympathetic nervous activity that, as described earlier, may account for the physiological effects of fear, anxiety, and acute stress. Norepinephrine neurons from the locus coeruleus also project to the amygdala, and the activation of postsynaptic norepinephrine $\beta_1$ adrenoceptors in the amygdala enhances anxiety. Again, the ability of SNRIs, which increase norepinephrine levels, to treat anxiety seems counterintuitive. But, just as desensitization of 5-HT$_{1A}$ autoreceptors ultimately facilitates reductions in anxiety, so does desensitization of $\beta_1$ adrenoceptors. Eventually, fewer active $\beta_1$ adrenoceptors result in a weaker activation of the amygdala, and subsequently, a reduction in anxiety (Duncan et al., 1989; Ordway et al., 1991).

As a final note, while 5-HT$_{1A}$ receptors might be implicated in the effects of antidepressant drugs for the treatment of anxiety, we must also keep in mind human genetic studies showing links between reduced serotonin membrane transporter functioning (the short allele discussed earlier in this chapter) and anxiety traits. Based on what we find from the pharmacological model for anxiolytic effects discussed in this section, one would expect *reduced* anxiety for those with reduced serotonin transporter function, since less reuptake should mean greater serotonin levels. Yet, genetic studies in mice lacking serotonin transporters suggest this is not the case. In serotonin transporter null mice, the activity of serotonin neurons appears

to be diminished, despite these mice having lower levels of somatodendritic 5-$HT_{1A}$ receptors, which should mean less inhibition of serotonin neurons (Fabre et al., 2000; Gobbi, Murphy, Lesch, & Blier, 2001). Findings such as these remind us that models to help explain the pharmacological actions of drugs may be different from mechanisms mediating the actual disorder.

## STOP & CHECK

1. Long-term administration with an SSRI or SNRI can desensitize 5-$HT_{1A}$ receptors, resulting in a(n) _____ in serotonin levels.
2. Long-term administration of an SNRI can desensitize $\alpha_2$ heteroceptors on serotonin neurons, resulting in a(n) _____ in serotonin levels.
3. Long-term administration of an SNRI can desensitize $\beta_1$ adrenoceptors in the amygdala, resulting in a(n) _____ in anxiety.

1. increase 2. increase 3. decrease

## CHAPTER SUMMARY

Anxiety disorders, which include specific phobias, panic disorder, agoraphobia, social anxiety disorder, and generalized anxiety disorder, and related disorders, including PTSD and OCD, are highly prevalent. The amygdala plays an important role in anxiety disorders. Other limbic system structures, including the hippocampus and cingulate cortex, might also play a role in anxiety disorders as demonstrated in studies using fear conditioning. The hypothalamic-pituitary-adrenal (HPA) axis mediates the feelings associated with panic attacks and mediates the body's response to long-term stress. Sustained stress leads to activation of the HPA axis and increased levels of cortisol, the body's stress hormone. Drugs effective for anxiety include anxiolytic drugs, antidepressant drugs, and 5-$HT_{1A}$ receptor agonists. Barbiturates, the first anxiolytic drugs, caused CNS depressant effects, carried a risk for respiratory failure, and had a high abuse liability. Barbiturates facilitated the effects of the inhibitory neurotransmitter GABA by binding to barbiturate sites on $GABA_A$ receptors. Benzodiazepines replaced barbiturates for the treatment of anxiety and are still used today. Benzodiazepines also are CNS depressants, but carry less risk of respiratory suppression and have a lower risk of abuse. Benzodiazepines facilitate the effects of GABA for $GABA_A$ receptors. Chronic administration of buspirone appears effective for generalized anxiety disorder. Beta blockers reduced the physiological fight-or-flight response associated with anxiety. Antidepressant drugs have become the first-line treatments for anxiety disorders largely because of their efficacy and low abuse liability.

## KEY TERMS

Fear 461
Anxiety 462
Specific phobias 462
Panic disorder 462
Panic attacks 462
Agoraphobia 462
Social anxiety disorder 462
Generalized anxiety disorder 462
Obsessive–compulsive disorder 463
Post-traumatic stress disorder (PTSD) 463
General adaptation syndrome 475
Cortisol 475
Hypothalamic–pituitary–adrenal (HPA) axis 475
Anxiolytic drug 477
Beta blocker (or beta receptor antagonist) 480

CHAPTER

15

# Antipsychotic Drugs

## Chapter Outline

- Schizophrenia
- Schizophrenia's Complex Neurobiological Profile
- A Brief History of Schizophrenia and Its Treatment
- Neurotransmission Hypotheses for Schizophrenia
- Typical and Atypical Antipsychotic Drugs
- Antipsychotic Drugs and Autism
- From Actions to Effects: Antipsychotic Drug Actions and Neurotransmission in Schizophrenia

## Learning Objectives

- Describe the symptoms and neurobiology of schizophrenia
- Compare and contrast the effects of typical and atypical antipsychotic drugs
- Compare and contrast the actions of typical and atypical antipsychotic drugs

## Schizophrenia

**Schizophrenia** is a severe, lifelong mental illness consisting of disturbed thinking, abnormal behavior, an inability to understand what is real, and an impaired processing of emotions. The symptoms of schizophrenia consist of either **positive symptoms** or **negative symptoms**. The terms *positive* and *negative* refer to the presence of abnormal behaviors or the reduction in normal behaviors, respectively. Examples of positive symptoms include hallucinations, delusions, and thoughts of persecution, whereas negative symptoms include reduced emotional responsiveness, social withdrawal, reduced movement, and lack of motivation.

The DSM-5 includes schizophrenia in the category "Schizophrenia Spectrum and Other Psychotic Disorders," which overall refers to disorders defined by delusions, hallucinations, disorganized speech and thinking, disorganized behavior, abnormal motor behavior, and/or negative symptoms (American Psychiatric Association, 2013a).

**Schizophrenia**
Severe, lifelong mental illness consisting of disturbed thinking, abnormal behavior, an inability to understand what is real, and an impaired processing of emotions

**Positive symptoms**
Addition of abnormal behaviors such as hallucinations, delusions, and thoughts of persecution in schizophrenia

**Negative symptoms**
Reduction of normal behaviors such as reduced emotional responsiveness, social withdrawal, reduced movement, and lack of motivation in schizophrenia

Schizophrenia consists of the most severe of these disorders and has at least two of the features listed in this category (at least consisting of delusions, hallucinations, or disorganized speech and thinking). The symptoms expressed must be highly disruptive for a period of at least six months.

Past versions of the DSM described five types of schizophrenia: (1) a *paranoid* type characterized by prominent positive symptoms; (2) a *catatonic* type characterized by predominantly negative symptoms, including immobility; (3) a *disorganized* type characterized by disorganized behaviors and silly or immature emotional expression; (4) an *undifferentiated* type that does not appropriately fit these other categories; and (5) a *residual* type for patients who now exhibit less prominent symptoms of schizophrenia, but did so in the past. Those who wrote the DSM-5 removed these distinctions because they believed that defining subtypes did not add value to making an overall schizophrenia diagnosis (American Psychiatric Association, 2013b).

Longitudinal studies find that 50–70 percent of individuals diagnosed with schizophrenia exhibit chronic symptoms; the remaining 30–50 percent of patients tend to exhibit residual features of schizophrenia (Bota, Munro, Nguyen, & Preda, 2011). Moreover, we find that approximately one-third of those with schizophrenia qualify as treatment-resistant patients. Those defined as having **treatment-resistant schizophrenia** exhibit no or minimal improvements after two trials with either a typical or an atypical antipsychotic drug, two types of antipsychotic drugs described later in this chapter.

**Treatment-resistant schizophrenia**
Patients with schizophrenia who exhibit minimal or no improvements after two trials with either typical or atypical antipsychotic drugs

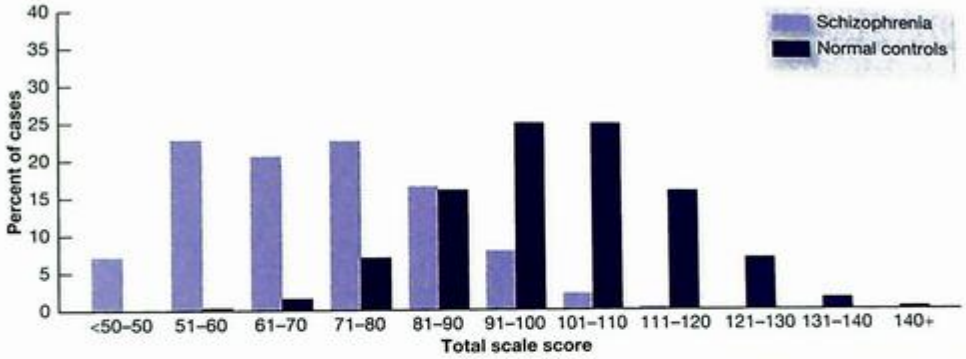
For patients with catatonic schizophrenia who do not respond to antipsychotic medication, physicians may prescribe benzodiazepines, which tend to show some efficacy for reducing catatonia (Ungvari, Kau, Wai-Kwong, & Shing, 2001). In addition to schizophrenia, other disorders in which catatonia may occur include depression, alcohol withdrawal, and acquired immunodeficiency syndrome (most often referred to as AIDS; occurs from infection by the human immunodeficiency virus, HIV) (Geoffroy, Rolland, & Cottencin, 2012; Starkstein et al., 1996; Volkow, Harper, Munnisteri, & Clother, 1987). AIDS can lead to inflammation in the brain, which in turn can cause a number of behavioral, cognitive, and physiological effects. In fact, those with AIDS can exhibit psychotic symptoms, which may be treated by antipsychotic medications (Lera & Zirulnik, 1999). In a study examining treatments for catatonia, Ungvari, Leung, Wong, and Lau (1994) evaluated the effects of the benzodiazepines lorazepam or diazepam in 18 patients found with catatonia. Some of the patients had catatonic schizophrenia, while other patients exhibited catatonia from depression, bipolar depression, or other mental disorders. In all but two of the patients, two days of benzodiazepine treatment led to reductions in catatonia.

Although clinicians diagnose schizophrenia based on the presence of positive and negative symptoms, researchers find striking and consistent impairments in cognitive functioning (Silver, Feldman, Bilker, & Gur, 2003). Nearly all individuals with schizophrenia have moderate to severe deficits in cognitive functioning, including working memory, reference memory, attention, and executive functioning, compared to the general population (Green, Kern, & Heaton, 2004; Keefe & Fenton, 2007; Wilk et al., 2004) (see **Figure 15.1**). Cognitive impairment may be present before the first episode of schizophrenia (Keefe & Fenton, 2007). Researchers find that cognitive impairment contributes to poor functional outcomes. **Functional outcomes** consist of a patient's inclusion into a community, behaving normally in social situations, and successfully employing psychosocial skills. Examples of functional outcomes in

**Functional outcomes**
A patient's inclusion into a community, behaving normally in social situations, and successfully employing psychosocial skills

**FIGURE 15.1 Cognitive Impairment in Schizophrenia**

Individuals with schizophrenia tend to score lower on tests for cognitive performance compared to healthy individuals. In this figure, patients with schizophrenia were compared to healthy controls on the Repeatable Battery for the Assessment of Neuropsychological Status, which measures memory, attention, and other aspects of cognitive functioning. Scores on the scale are plotted in increments of 10 on the *x*-axis. The percentage of participants scoring within each range is plotted from the *y*-axis. The average score for healthy participants was 100, and the average score for individuals with schizophrenia was 70, a score that only two percent of the healthy participants had.




*Source:* Keefe, R. S., & Fenton, W. S. (2007). How should DSM-5 criteria for schizophrenia include cognitive impairment? *Schizophr Bull*, 33(4), 912–920. doi:sbm046 [pii] 10.1093/schbul/sbm046, p. 8. By permission of Oxford University Press.

schizophrenia include employability, ability to conduct daily living activities, and the ability to form friendships (Green, 1996; Green, Kern, Braff, & Mintz, 2000).

Many patients with schizophrenia demonstrate a **sensory-gating deficit** that is characterized by a diminished capacity to filter out unimportant stimuli in their environment. Attendance to these unimportant stimuli may lead to misperceptions of their environment, possibly facilitating delusional behavior (Adler et al., 1998). Researchers assess sensory-gating deficits in schizophrenia by using a prepulse inhibition procedure as described in **Box 15.1**.

**Sensory-gating deficit**
A schizophrenic's diminished capacity to filter out unimportant stimuli in his or her environment

# BOX 15.1

## PREPULSE INHIBITION

The prepulse inhibition procedure consists of determining one's ability to demonstrate a weaker reflexive response to a sudden stimulus after exposure to a weaker form of the stimulus immediately before. In humans, researchers normally use auditory stimuli and assess eyeblink as the response, as measured in intensity using measures of muscle movement around the eye.

For example, Braff, Swerdlow, and Geyer (1999) assessed the effects of a brief 112-decibel blast of white noise on intensity of eyeblink startle response

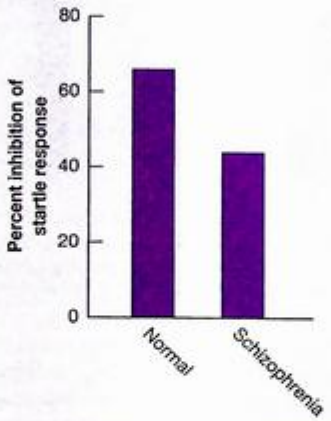
*(Continued)*

(Continued)

(**Box 15.1 Figure 1**). Then during selected trials, a quieter pulse of white noise occurred 40 milliseconds before the 112-decibel white noise. For those without schizophrenia, the preceded noise significantly diminished their subsequent startle to the louder noise that immediately followed. Yet, individuals with schizophrenia had a significantly poorer reduction in startle response under these same circumstances. We infer from these findings that those with schizophrenia have a weaker ability to filter out these auditory stimuli.

**BOX 15.1 FIGURE 1** **Prepulse Inhibition Deficits in Schizophrenia**

Individuals with schizophrenia demonstrated a diminished ability to inhibit a startle response compared to normal controls in a prepulse inhibition test.




*Source:* Data from Braff et al. (1999).

**Cognitive dysmetria**
Abnormalities in processing, coordinating, and responding to information

A theory known as cognitive dysmetria attempts to link facets of sensory processing with cognitive functioning and the manifestation of positive and negative symptoms. **Cognitive dysmetria** consists of abnormalities in processing, coordinating, and responding to information. As a result of cognitive dysmetria, one may perceive hallucinations, form delusions, exhibit odd or disorganized speech, incorrectly respond to emotional stimuli, have impaired attention, and exhibit other characteristics found in schizophrenia (Andreasen, Paradiso, & O'Leary, 1998).

A first diagnosis for schizophrenia is usually found in one's late teens or early 20s. We seldom find schizophrenia occurring before puberty or after age 40 (Lewis & Lieberman, 2000). Schizophrenia is relatively prominent among psychiatric disorders, affecting one percent of the world's population. This equates

to approximately 3 million individuals in the United States (Regier et al., 1993). The prevalence of schizophrenia occurs equally in males and females, although males may develop this disorder two to four years earlier than females and exhibit more severe symptoms. A modestly increased prevalence of schizophrenia occurs in northern geographic regions and for individuals born during winter months, the latter possibly related to winter diseases such as influenza (Davies, Welham, Chant, Torrey, & McGrath, 2003).

Schizophrenia provides a significant societal impact, with no more than 73 percent of individuals able to find any employment and only 14.5 percent of individuals finding competitive employment (Rosenheck et al., 2006). Depression rates among individuals with schizophrenia are high, with as many as 10 percent committing suicide each year (Caldwell & Gottesman, 1990; Miles, 1977; Pompili et al., 2007). In general, researchers find a 16- to 18-year shorter life span among those with schizophrenia compared to the general population (Laursen, 2011).

Schizophrenia clearly has a genetic basis, although this is not the only determining factor. In the general population, as noted above, we find a one percent rate of prevalence. This risk factor increases slightly to about two to four percent when there is a cousin, uncle or aunt, or nephew or niece with schizophrenia. However having one parent with schizophrenia increases the risk to 13 percent and having both parents with schizophrenia increases the risk to about 50 percent. Having an identical twin with schizophrenia also provides a 50-percent chance of developing schizophrenia (**Figure 15.2**). The remaining risks for developing schizophrenia come from the environment, which may consist of responses to stress, life events, or other factors (Tsuang, 2000; van Os, Kenis, & Rutten, 2010).

In the years before a first diagnosis of schizophrenia, patients usually exhibit subtle, early signs of schizophrenia. These pre-schizophrenia signs are collectively referred to as the **prodromal phase of schizophrenia**, which is characterized by schizophrenia-like symptoms that occur less frequently and with less severity than the symptoms found in schizophrenia. These include, in particular, deficits in working memory, attention, sensory gating, and sociability. Of these, attention impairment appear most predictive of the prodromal phase. In addition to these behavioral and cognitive features, those identified with prodromal phase characteristics also exhibit reduced volume of cortical gray matter (Stone et al., 2009).

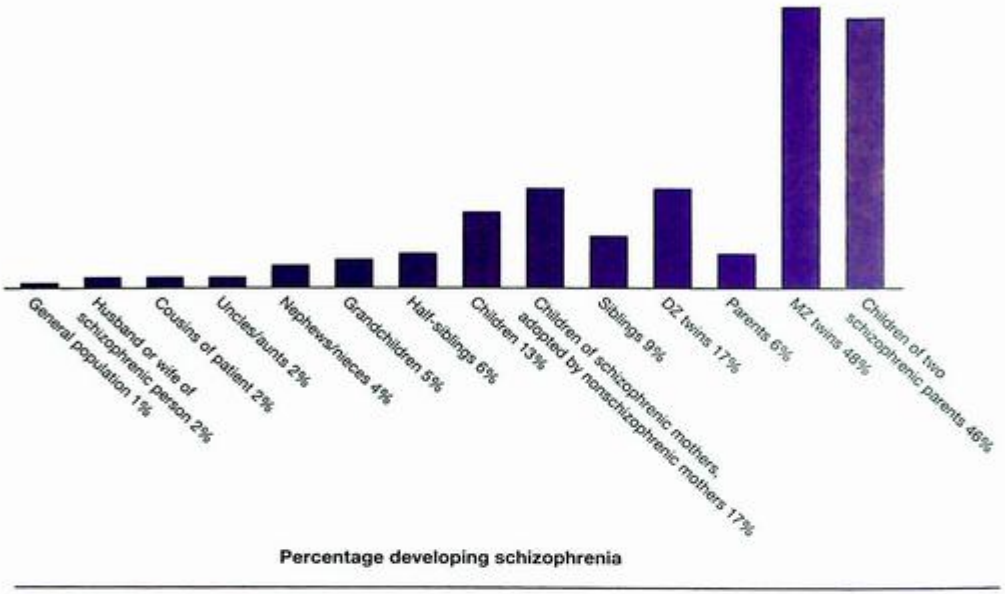
## STOP & CHECK

1. Reduced emotional expression and social isolation are both examples of _____ symptoms of schizophrenia.
2. Although not considered part of the diagnosis criteria, impairments in _____ functioning are commonly found in patients with schizophrenia.

1. negative 2. cognitive

**FIGURE 15.2 Genetic Concordance in Schizophrenia**

The risk of developing schizophrenia increases with genetic closeness to a relative who has schizophrenia.




*Source:* Based on data from Gottesman (1991).

## Schizophrenia's Complex Neurobiological Profile

Schizophrenia derives from a complexity of neurobiological traits, including genetic abnormalities, reduced volume of brain structures, and abnormal connectivity among brain structures (Lewis & Lieberman, 2000; Ross, Margolis, Reading, Pletnikov, & Coyle, 2006). Yet, most of these characteristics remain to be fully understood (Ross et al., 2006).

Among the many genes studied for a risk of schizophrenia, we find perhaps the most evidence implicating the *disrupted in schizophrenia 1* (DISC1) gene (Hodgkinson et al., 2004; Roberts, 2007). Associations occur between abnormal DISC1 genes and occurrence of schizophrenia in Scottish and Finnish individuals (Ekelund et al., 2001; Millar et al., 2000). The DISC1 gene encodes for the DISC1 protein, which plays an important role in a cascade of signalling events that take place within neurons, as well as the development of neurons (Mao et al., 2009). In particular, DISC1 genes may affect cell migration, which can lead to architectural abnormalities in cellular networks (Wong & Van Tol, 2003).

Although monozygotic twins have, by definition, identical genetic makeups, epigenetic factors may explain why one twin may develop schizophrenia while the other twin does not. Castellani, Melka, Gui, O'Reilly, and Singh (2015) examined monozygotic twins among whom only one twin had schizophrenia. They found many instances in the expression of genes of the twin with schizophrenia. These differences in expression were found for DISC1 as well as a host of other genes potentially implicated in schizophrenia (which are beyond the scope of this textbook to cover).

**Review!** Epigenetics is the study of mechanisms of gene expression not involving alterations to DNA sequences (Chapter 2).

Structural differences in schizophrenia may vary across patients as shown through inconsistent findings across neuroimaging studies. The most consistent observations suggest reduced volume sizes of structures in the left hemisphere and temporal lobe. Studies also find reduced volume of the frontal lobe, including the prefrontal cortex, and the thalamus in the left hemisphere, and reduced connectivity from the thalamus to the cerebellum (Byne, Hazlett, Buchsbaum, & Kemether, 2009; Ross et al., 2006). The cognitive dysmetria theory, in particular, refers to dysfunctions in connectivity between the thalamus and the cerebellum and the thalamus and cerebral cortex as contributing to abnormal sensory processing, timing functions, and error processing, which may lead to many of the symptoms and cognitive disturbances described earlier (Andreasen et al., 1998; Barch, 2014). Furthermore, imaging and post-mortem studies tend to reveal a modest volume reduction of the hippocampus in both hemispheres (Lewis & Lieberman, 2000). Functional imaging studies also reveal abnormal levels of activity in the hippocampus during auditory hallucinations, memory tasks, and rest (Heckers, 2001).

Volume reductions may arise from altered circuitry within these structures. Post-mortem studies find a possible disorganization of axons in cortical white matter (Akbarian et al., 1996; Arnold, Talbot, & Hahn, 2005). Individuals with schizophrenia also appear to have fewer projections from the thalamus going to the prefrontal cortex (Lewis & Lieberman, 2000). The result of these or other possible altered circuitry may cause differences in neurotransmission, which we consider in the context of antipsychotic drug actions later in this chapter.

Taken together, researchers see the many different abnormalities described above as support for the neurodevelopmental hypothesis for schizophrenia. The **neurodevelopmental hypothesis** for schizophrenia states that abnormal nervous system development leads to irregular neuronal signalling in the brain, resulting in the characteristics of schizophrenia (Weinberger, 1996). As Lewis and Lieberman (2000) describe, genetics causes alterations in neuronal growth and development, which likely impacts synaptogenesis and myelination, before and after birth. Recent studies, as noted earlier, indicate that epigenetic factors may be critical in the expression of genes leading to such potential abnormalities in neuronal growth and development (Castellani et al., 2015). These abnormalities might eventually cause

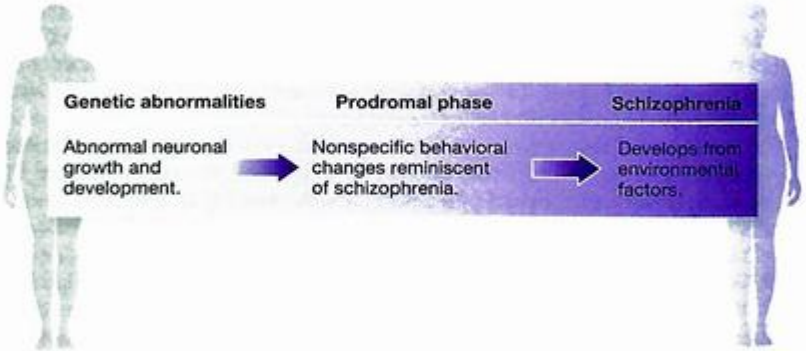
**Neurodevelopmental hypothesis** Hypothesis for schizophrenia stating that abnormal nervous system development leads to irregular neuronal signalling in the brain, resulting in the characteristics of schizophrenia

the prodromal phase of schizophrenia, as described earlier, during adolescence. The transition from a prodromal phase to the full onset of schizophrenia may later arise in reaction to environmental factors, such as involvement in prolonged stressful situations or using substances of abuse (**Figure 15.3**).

For these particular reasons, researchers have attempted to *prophylactically* treat those at high risk for schizophrenia and demonstrating characteristics of prodromal schizophrenia. A **prophylactic treatment** consists of a treatment to prevent a disorder from occurring. A first-line approach for prodromal schizophrenia consists of cognitive behavior therapy. Those in cognitive behavior therapy learn to monitor their thoughts and behaviors, and from this therapy, statistically fewer patients developed formal psychotic symptoms than was otherwise predicted. Studies have also evaluated antipsychotic drug treatment with a goal to reduce weak psychotic symptoms and prevent conversion to schizophrenia. Generally, antipsychotic drugs reduce prodromal psychotic symptoms and appear in some studies to prevent schizophrenia, although cognitive behavior therapy appears to be at least as effective. Also, exposing adolescents to the adverse effects of antipsychotics if unnecessary raises important ethical questions. On the one hand, patients face the risk of metabolic and cardiovascular effects, whereas on the other hand, an effective prophylactic treatment might prevent the occurrence of a lifelong disabling disorder (Conroy, Francis, & Hulvershorn, 2018).

**FIGURE 15.3** **Neurodevelopmental Hypothesis of Schizophrenia**

Schizophrenia may develop from a combination of genetic and environmental factors. Genetic factors may alter the normal development, growth, and connectivity among neurons, which may predispose an individual to develop prodromal features of schizophrenia. A response to environmental events may cause someone to shift from the prodromal phase to full onset of schizophrenia.




*Source:* Adapted from Lewis and Lieberman (2000).

## A Brief History of Schizophrenia and Its Treatment

Stories of madness have been documented throughout human history, but the first clinical diagnosis for schizophrenia was made only in 1871 by Ewald Hecker in Görlitz, Germany. Hecker gave several psychotic young patients a diagnosis of *hebephrenia*, a term coined by his clinical director, Karl Kahlbaum. In 1893, Emil Kraepelin first named this disorder *dementia praecox*, noting the striking cognitive decline by relatively young individuals, particularly compared to dementias he studied in the elderly. Some years later, in 1911, Eugen Bleuler coined the term *schizophrenia* because of what he saw as a "splitting of psychic functions" in this disorder and a consistent lack of increasing cognitive decline like that seen in Alzheimer's disease (Shorter, 1997). Lacking a clear biological cause coupled with the rise of psychoanalysis in psychiatry, the psychiatric community in the early to mid-20th century was seeking causes of schizophrenia in one's upbringing. One of the most notorious of these now-abandoned notions was the *schizophrenogenic mother* concept—that is, bad mothering causes schizophrenia (Hartwell, 1996; Neill, 1990).

Early attempts to treat schizophrenia appear cruel by today's standards. During the early 20th century, psychiatric staff often employed confinement methods as purported treatments, which often included the use of an isolation cell or straitjacket. Staff members also restrained patients in ice baths for hours or days at a time. Some psychiatrists induced fevers in their patients, which resulted in a temporary abatement of symptoms afterward. By the 1930s, convulsive shock therapies, using either insulin or electricity, sometimes offered real gains in symptom remission, although only temporarily and with significant risk to the patient (Shorter, 1997).

Also during this time, the first of a series of techniques, collectively referred to as *frontal lobotomies*, began to be offered as a long-lasting treatment for schizophrenia, although they provided no symptom improvements and were made at great cost to the patient's health, assuming the patient even survived the procedure (Freeman & Watts, 1945; Shorter, 1997). There were several different ways developed to produce frontal lobotomies, but all of these methods involved penetrating the frontal lobe with an instrument, often simply a rod, and then moving the instrument around to destroy brain tissue. The result was often described as a state of drowsiness and disorientation. There also was significant risk of death from these procedures from hemorrhaging in the brain. Walter Freeman is most noted for promoting frontal lobotomy techniques for treating schizophrenia, and he is particularly known for the *transorbital leucotomy*. The first procedures involved the use of ordinary ice picks, thus leading to so-called ice-pick lobotomies (**Figure 15.4**). During this procedure, Freeman punched the instrument up into the frontal lobe through the inner corner of the eye socket. He then moved it around within the frontal lobe to destroy brain tissue (Kucharski, 1984; Shorter, 1997).

Some years later, in 1952, Henri Laborit administered a pre-anesthetic agent called *chlorpromazine* to manic patients at St. Anne's Hospital in Paris in the hope that it might calm his patients. He indeed found them calmer, yet he also noticed an abatement of symptoms among those with psychosis as well. The efficacy of chlorpromazine specifically for schizophrenia was soon studied by Jean Delay, Pierre Deniker, and Jean-Marie Harl, who published their findings on the effects

**FIGURE 15.1 Walter Freeman Performing a Transorbital Leucotomy**

Photo of Walter Freeman performing a transorbital leucotomy, more generally referred to as an "ice-pick lobotomy," in a patient.

Getty Images/Bettmann

of chlorpromazine in psychotic patients in that same year (Delay, Deniker, & Harl, 1952). Without question this discovery revolutionized the treatment for mental illnesses and might very well have led to a Nobel Prize for its discoverers. Yet, a bitter dispute erupted between those claiming to have made the discovery first—Laborit claimed first to find a reduction in psychosis while Delay and Deniker claimed first to formally study it. In fact, between Delay and Deniker, Deniker was widely recognized as the clinician evaluating chlorpromazine's antipsychotic effects. We find this demonstrated when the Lasker Prize for Clinical Medical Research—often considered the prelude to the Nobel Prize—was given to Laborit and Deniker in 1957, excluding Delay. We do not find Jean-Marie Harl mentioned in these disputes because he was primarily a trainee at the time, but also because he died soon after from a climbing accident (science prizes tend not to be given posthumously). Unfortunately, as a clinical trainee, Harl likely did most of the study's clinical work (Healy, 2002).

Yet, neither Laborit nor Deniker received a Nobel Prize. We're left to speculate a bit on why this might be. Edward Kunz (2014), who knew and collaborated with Laborit on unrelated projects, suggested that French clinicians disagreed with Laborit's various medical theories and helped to dissuade the nominating committee

from granting Laborit a Nobel Prize. Adding to this, according to Healy (2002), Delay served on the Nobel Prize nominating committee and likely sought to prevent awarding the prize to Laborit. If Laborit were not to get it, then it's unlikely that they would have given the prize to Deniker instead, whom the Lasker Prize committee had considered a co-discoverer.

Chlorpromazine and therapeutically similar drugs that followed revolutionized the treatment of schizophrenia. Of the procedures predating the antipsychotic drugs, only electroconvulsive shock therapy remains, although it is a substantially improved version compared to the 1930s and 1940s and is used as a last resort for those patients who fail to improve with antipsychotic drug treatment (Chanpattana & Sackeim, 2010).

## Neurotransmission Hypotheses for Schizophrenia

Most theories concerning the neuropathology of schizophrenia consider abnormalities in dopamine and glutamate neurotransmission. Much of what we know about these irregularities comes from studying the actions of antipsychotic drugs and experimentally inducing temporary psychotic states in healthy human volunteers with dopaminergic and glutamatergic drugs.

The first well-established hypothesis is the **dopamine hypothesis for schizophrenia**, which states that positive symptoms arise from excessive dopamine release in the limbic system (Meltzer & Stahl, 1976) (**Figure 15.5**). The hypothesis derives from the discovery that antipsychotic drugs act as antagonists for $D_2$ receptors and that amphetamine, through increasing dopamine release, causes psychotic symptoms (Seeman & Lee, 1975; Wallis, McHarg, & Scott, 1949). As shown in **Figure 15.6**, antipsychotic drug doses effective for schizophrenia correlate highly to their strength of binding to $D_2$ receptors (Seeman, 2005; Seeman & Lee, 1975).

**Dopamine hypothesis (for schizophrenia)** Hypothesis for schizophrenia stating that positive symptoms arise from excessive dopamine release in the limbic system

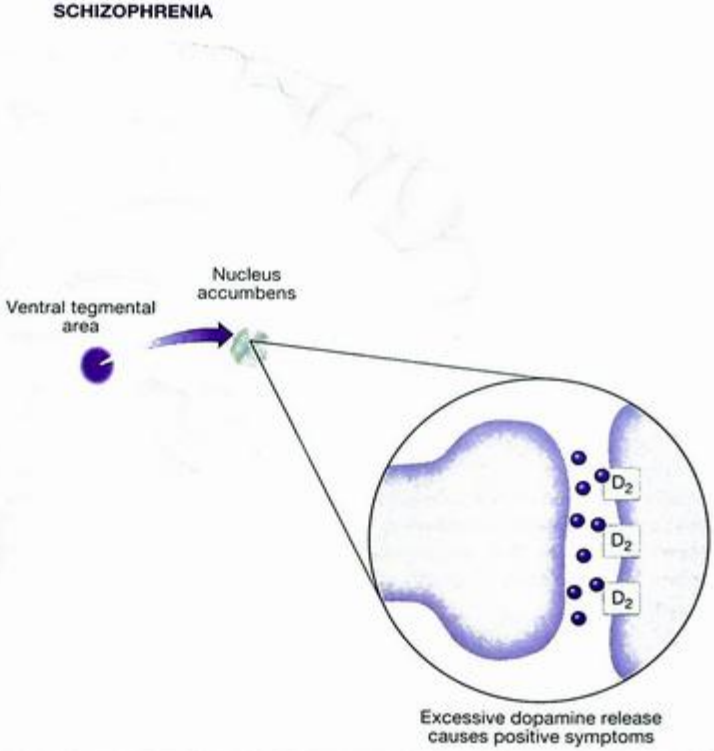
Although we still find the dopamine hypothesis useful for understanding antipsychotic drug actions, we also find glutamate dysregulated in schizophrenia. According to the **glutamate hypothesis for schizophrenia**, diminished levels of glutamate release throughout the cerebral cortex and limbic system may lead to the symptoms of schizophrenia (Paz, Tardito, Atzori, & Tseng, 2008; Sesack, Carr, Omelchenko, & Pinto, 2003). Support for this hypothesis comes from human drug overdose cases and experimental studies with the dissociative anesthetics phencyclidine and ketamine (Jacob, Carlen, Marshman, & Sellers, 1981; Krystal et al., 1994). An appealing feature of this hypothesis is that acute administration of ketamine and phencyclidine cause users to exhibit behaviors similar to negative symptoms and cognitive impairment, as well as positive symptoms, in schizophrenia. We show how the glutamate and dopamine hypotheses can be integrated in complementary ways in the "From Actions to Effects" section at the end of this chapter.

**Glutamate hypothesis (for schizophrenia)** Hypothesis for schizophrenia stating that diminished levels of glutamate release throughout the cerebral cortex and limbic system may lead to the symptoms of schizophrenia

**Review!** The dissociative anesthetic drugs ketamine and phencyclidine function as antagonists for glutamate NMDA receptors (Chapter 12).

**FIGURE 15.5** **Dopamine Hypothesis for Schizophrenia**

According to the dopamine hypothesis for schizophrenia, increased dopamine release from mesolimbic dopamine neurons causes the positive symptoms of schizophrenia. Mesolimbic dopamine neurons terminate in structures of the limbic system such as the nucleus accumbens shown here.



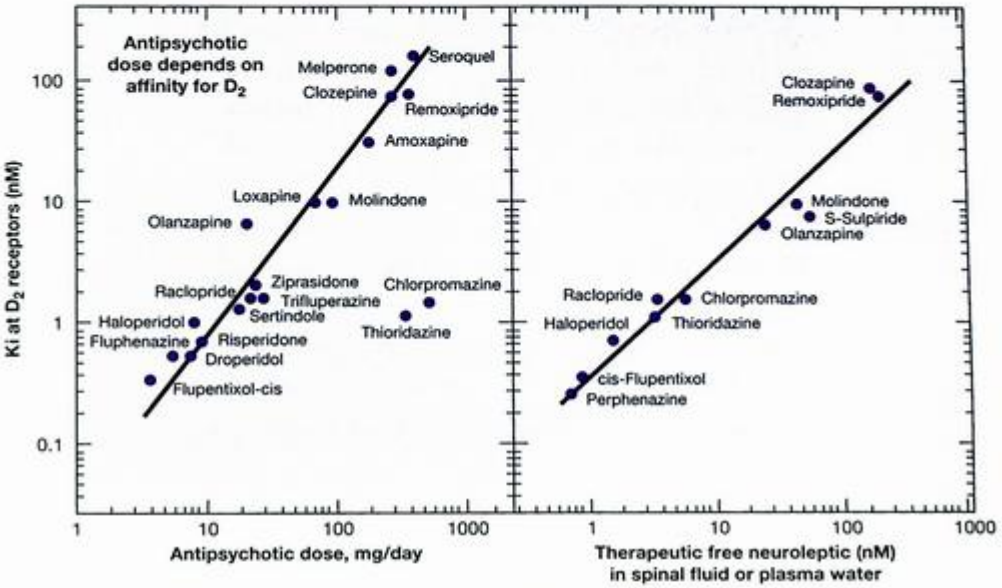

## STOP & CHECK

1. The first antipsychotic drug was _____, which Laborit first provided to manic patients, and Delay, Deniker, and Harl formally evaluated in patients with schizophrenia.
2. The hypothesis for positive symptoms in schizophrenia states elevated concentrations of _____ are found in the limbic system.

1. chlorpromazine 2. dopamine

**FIGURE 15.6** **Dopamine $D_2$ Receptors and Therapeutic Efficacy**

There is a strong association between strength of binding for the $D_2$ receptor (*y*-axis) and the dosage of an antipsychotic drug necessary to produce antipsychotic effects (*x*-axis).




*Source:* Adapted by permission from Macmillan Publishers Ltd: "Antipsychotic drug doses and neuroleptic/dopamine receptors," by P. Seeman, T. Lee, M. Chau-Wong, and K. Wong, *Nature*, 261, 1976, pp. 717–719.

## Typical and Atypical Antipsychotic Drugs

We divide the wide variety of antipsychotic drugs into two broad categories: typical antipsychotic drugs and atypical antipsychotic drugs (**Table 15.1**). However, many different names are used to describe these categories. Researchers and clinicians may instead refer to typical antipsychotic drugs as *first-generation* or *classical* antipsychotic drugs. We also find the term *neuroleptic* synonymous with a typical antipsychotic drug, although many people misapply this term to describe all types of antipsychotic drugs. Atypical antipsychotic drugs may be called *second-generation* or *novel* antipsychotic drugs. Finally, some researchers describe a third class of antipsychotic drugs, generally referred to as *third-generation* antipsychotic drugs, to describe newer agents that may differ pharmacologically from drugs in these other categories (Meltzer, 2002). This chapter will first describe the development and pharmacology of typical antipsychotic drugs and then those of atypical antipsychotic drugs. Finally, it follows with a discussion about third-generation antipsychotic drugs.

**TABLE 15.1 Selected Antipsychotic Drugs**

| Typical Antipsychotic Drugs | Atypical Antipsychotic Drugs |
|---|---|
| Chlorpromazine (*Thorazine*) | Amisulpride (*Solian*) |
| Droperidol (*Inapsine*) | Aripiprazole (*Abilify*)* |
| Fluphenazine (*Prolixin*) | Asenapine (*Saphris*) |
| Haloperidol (*Haldol*) | Cariprazine (*Vraylar*) |
| Loxapine (*Loxitane*) | Clozapine (*Clozaril*) |
| Molindone (*Moban*) | Iloperidone (*Fanapt*) |
| Perazine (*Taxilan*) | Lurasidone (*Latuda*) |
| Perphenazine (*Trilafon*) | Olanzapine (*Zyprexa*) |
| Pimozide (*Orap*) | Paliperidone (*Invega*) |
| Prochlorperazine (*Compazine*) | Quetiapine (*Seroquel*) |
| Thiothixene (*Navane*) | Risperidone (*Risperdal*) |
| Thioridazine (*Mellaril*) | Ziprasidone (*Geodon*) |
| Trifluoperazine (*Stelazine*) | |

*Sometimes referred to as a "third-generation" antipsychotic drug.

## Typical Antipsychotic Drugs: The First Medications for Schizophrenia

**Typical antipsychotic drugs (or first-generation or classical antipsychotic drugs)** Class of antipsychotic drugs that reduce the positive symptoms of schizophrenia, have weak efficacy for negative symptoms and cognitive impairment, and produce extrapyramidal side effects at therapeutic doses

As noted previously, the first of the typical antipsychotic drugs was chlorpromazine. A number of chlorpromazine-like drugs followed, including the typical antipsychotic *haloperidol*, a butyrophenone compound synthesized in 1958. As a class, **typical antipsychotic drugs** reduce the positive symptoms of schizophrenia, have weak efficacy for negative symptoms and cognitive impairment, and produce extrapyramidal side effects at therapeutic doses (**Table 15.2**). The pharmacological actions of antipsychotic drugs derive from antagonism of dopamine $D_2$ receptors. Typical antipsychotic drugs may require as long as six to eight weeks to produce full efficacy (Agid, Kapur, Arenovich, & Zipursky, 2003; Emsley, Rabinowitz, & Medori, 2006).

**Figure 15.7** shows these actions using the dopamine hypothesis of schizophrenia. As previously noted, this hypothesis consists of elevated levels of dopamine and its subsequent activation of dopamine $D_2$ receptors. Typical antipsychotic drugs reduce positive symptoms by counteracting elevated dopamine release through antagonism of $D_2$ receptors. These actions also account for extrapyramidal side effects (Meltzer & Stahl, 1976).

**TABLE 15.2 Typical Versus Atypical Antipsychotic Drug Effects and Mechanisms**

| | Typical Antipsychotic | Atypical Antipsychotic |
|---|---|---|
| Positive symptoms | Effective | Effective |
| Negative symptoms | Generally ineffective | Modestly effective |
| Cognitive impairment | Generally ineffective | Modestly effective |
| Extrapyramidal side effects | Occur at therapeutically effective doses. Managed by an anticholinergic drug. | Unlikely to occur at therapeutically effective doses |
| Tardive dyskinesia | Likely to develop after long-term use | Unlikely |
| Mechanism of action | Mainly through blockade of dopamine $D_2$ receptors | Through blockade of $D_2$ receptors and serotonin ($5\text{-}HT_{2A}$) receptors. However, many other receptors implicated in these effects. |

**Extrapyramidal side effects (EPS)** consist of tremor, muscle rigidity, and involuntary movements (Owens, 1999). As we see in Figure 15.7, the nigrostriatal dopamine pathway, which terminates in the basal ganglia, likely functions normally in schizophrenia. $D_2$ receptor antagonism reduces dopamine neurotransmission in this pathway, causing diminished control of movement. In many ways, EPS resembles the features of Parkinson's disease, which also derive from disrupted dopamine neurotransmission in this pathway.

**Extrapyramidal side effects (EPS)**
Adverse effects consisting of tremor, muscle rigidity, and involuntary movements associated with antipsychotic drugs.

Today, physicians seldom prescribe typical antipsychotic drugs for schizophrenia, but the low costs of these medications make them more readily available in economically impoverished parts of the world. For patients who are treated with a typical antipsychotic drug, physicians usually also prescribe a muscarinic receptor antagonist such as *benztropine* to reduce EPS severity (e.g., Brune et al., 1962). Unfortunately, muscarinic receptor antagonists further impair cognitive functioning in schizophrenia (Spohn & Strauss, 1989; Veselinović et al., 2015). Long-term usage with a typical antipsychotic drug, even when also prescribed with an anticholinergic drug, may result in an EPS-related condition called *tardive dyskinesia*.

**Tardive dyskinesia** is a motor disorder that affects muscles primarily around the mouth and other parts of the face. Characteristic features of tardive dyskinesia include facial ties and rhythmic, involuntary movements of the jaw such as chewing or teeth grinding, involuntary use of the tongue such as in lip licking, or excessive lip smacking and pursing. These adverse effects may not occur until after a patient

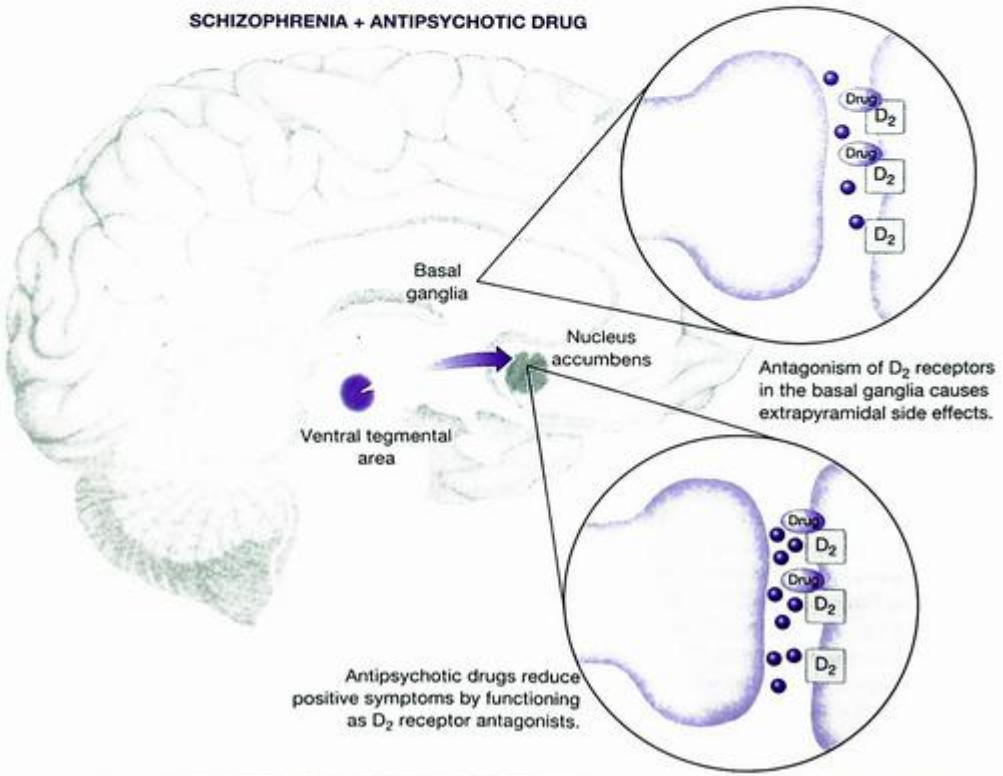
**Tardive dyskinesia**
Motor disorder primarily affecting muscles of the face that may occur after long-term antipsychotic drug use.

## Drug Profile: benztropine (or benzatropine)

| | |
|---|---|
| Brand name | *Cogentin* |
| Properties | Antagonist for cholinergic muscarinic receptors |
| Uses | Used to reduce extrapyramidal side effects from antipsychotic drugs |
| Similar drugs for treating EPS | Trihexyphenidyl (*Artane*) |

**FIGURE 15.7** **Antipsychotic $D_2$ Receptor Antagonism and Positive Symptoms**

Antipsychotic drugs reduce the positive symptoms of schizophrenia by acting as an antagonist for $D_2$ receptors, which counteracts the activity of mesolimbic dopamine neurons. Yet, antagonism of $D_2$ receptors impairs normal dopamine neurotransmission in the basal ganglia, leading to extrapyramidal side effects.



stops taking the medication. In fact, tardive dyskinesia can persist for months and even years after cessation from typical antipsychotic treatment (Owens, 1999).

Typical antipsychotic drugs also may produce neuroleptic malignant syndrome. Some of the symptoms of **neuroleptic malignant syndrome** resemble those of influenza, including sweating and fever, whereas other symptoms include blood pressure changes, autonomic nervous system irregularities such as changes in heart and breathing rate, and muscle rigidity (Caroff, 1980). These symptoms are severe and life threatening; any appearance tends to occur during the first few weeks of treatment. In nearly all cases, EPS also occurs with neuroleptic malignant syndrome (Addonizio, Susman, & Roth, 1987).

**Neuroleptic malignant syndrome**
Flu-like symptoms such as sweating, fever, and other symptoms such as blood pressure changes and autonomic nervous system irregularities induced by antipsychotic drugs

Typical antipsychotic drugs also are noted for **hyperprolactinemia**, which occurs from abnormally high blood levels of prolactin over prolonged periods of time. The symptoms of hyperprolactinemia include reduced lactation, loss of libido, disruptions in menstrual cycles, erectile dysfunction, and hypogonadism. Dopamine $D_2$ receptors regulate the release of prolactin from the anterior hypothalamus (Meltzer, Koenig, Nash, & Gudelsky, 1989).

**Hyperprolactinemia**
Disorder characterized by abnormally high blood levels of prolactin over prolonged periods of time, resulting in reduced lactation, loss of libido, disruptions in menstrual cycles, erectile dysfunction, and hypogonadism

In addition to the effects of typical antipsychotic drugs in schizophrenia, many of the typical antipsychotic drugs produce *antiemetic* effects. **Antiemetics** are drugs that reduce nausea and vomiting. Given these properties, typical antipsychotic drugs might be given with general anesthetics, to prevent vomiting during surgery, or be given to cancer patients on chemotherapy, which commonly produces nausea and vomiting. Nausea and vomiting occur from activation of the **chemoreceptor trigger zone**, an area in the medulla unprotected by the blood–brain barrier that receives inputs from substances in the blood. The chemoreceptor trigger zone sends signals, involving in part dopamine neurotransmission mediated by dopamine $D_2$ receptors, to the **area postrema** in the medulla, which elicits vomiting. Many typical antipsychotic drugs, which again serve as dopamine $D_2$ receptor antagonists, may block signals from the chemoreceptor trigger zone to the area postrema, thereby preventing vomiting. Some typical antipsychotic drugs also act as antagonists for 5-$HT_3$ receptors, a receptor action particularly linked to antiemetic effects (Jordan, Gralla, Jahn, & Molassiotis, 2014).

**Antiemetic**
Drugs that reduce nausea and vomiting

**Chemoreceptor trigger zone**
Area in the medulla unprotected by the blood–brain barrier receptive to substances in the blood or cerebrospinal fluid that, when activated, sends inputs to the area postrema to produce vomiting

**Area postrema**
Area in the medulla that produces vomiting

## STOP & CHECK

1. The primary pharmacological action thought responsible for the therapeutic effects of typical antipsychotic drugs consists of antagonism of _____ receptors.
2. In addition to primarily treating positive symptoms of schizophrenia, typical antipsychotic drugs also produce _____ at therapeutic doses.
3. A severe condition known as _____ syndrome consists of flu-like and other symptoms that can occur from treatment with antipsychotic drugs.
4. Typical antipsychotic drugs might produce antiemetic effects through antagonism of $D_2$ receptors, which reduces neurotransmission from the chemoreceptor trigger zone to the _____.

1. dopamine $D_2$, 2. extrapyramidal side effects, 3. neuroleptic malignant, 4. area postrema

## Atypical Antipsychotic Drugs: First-Line Treatments for Schizophrenia

*Clozapine (Clozaril)* was the first atypical antipsychotic drug. It was synthesized in 1959 only a few years after the discovery of chlorpromazine. Yet, researchers disregarded clozapine as an antipsychotic drug at first because of a lack of EPS in animal models. In other words, because all known antipsychotic drugs at the time produced EPS in humans, researchers identified potential antipsychotic drugs by their ability to produce EPS in animals. Thus, we do not find clozapine used clinically for schizophrenia until the 1970s and 1980s (Hippius, 1989; Matz, Rick, Thompson, & Gershon, 1974). The remarkable efficacy of clozapine led to the development of many other atypical antipsychotic drugs, including *olanzapine (Zyprexa)* and *risperidone (Risperdal)* (Table 15.1). As a class, **atypical antipsychotic drugs** reduce positive and negative symptoms and carry a low risk of EPS at therapeutic doses. Like typical antipsychotic drugs, atypical antipsychotic drugs may also require as long as six to eight weeks to produce full efficacy (Agid et al., 2003; Emsley et al., 2006).

**Atypical antipsychotic drugs (or second-generation or novel antipsychotic drugs)** Antipsychotic drugs that reduce positive and negative symptoms and carry a low risk of EPS at therapeutic doses

From clinical studies, we find that atypical antipsychotic drugs produce modest to moderate gains in negative symptoms. Moreover, clinical studies find consistent, albeit also modest, gains in cognitive functioning (Meltzer & McGurk, 1999; Woodward, Purdon, Meltzer, & Zald, 2005). Thus, we find some improvement in functional outcomes after atypical antipsychotic drug treatment, although it is less than desired (Green, Kern, Braff, & Mintz, 2000; Kaneda, Jayathilak, & Meltzer, 2010). Atypical antipsychotic drugs may also reduce depression in schizophrenia, and clinical studies find that clozapine, olanzapine, and risperidone reduce suicide risk among individuals with schizophrenia (Barak, Mirecki, Knobler, Natan, & Aizenberg, 2004; Meltzer, 2001). We also find improvements from some atypical antipsychotic drugs for *treatment-resistant* schizophrenia. Clozapine, for example, provides significant clinical improvement in 70 percent of treatment-resistant patients (Kane, Honigfeld, Singer, & Meltzer, 1988).

Atypical antipsychotic drugs carry the risk of serious adverse effects. As already noted, atypical antipsychotic drugs are capable of treating schizophrenia at doses that do not produce EPS. However, most atypical antipsychotic drugs will produce EPS at a sufficiently high dose. Atypical antipsychotic drugs also carry a risk of neuroleptic malignant syndrome (Trollor, Chen, & Sachdev, 2009). Although having lower risk than typical antipsychotic drugs, atypical antipsychotic drugs may produce hyperprolactinemia. Thus, when compared to typical antipsychotic drugs, atypical antipsychotic drugs have a lower risk, but not a complete absence of these adverse effects.

Clinicians carefully monitor for three other types of adverse effects. First, many atypical antipsychotic drugs produce significant increases in body weight (Kroeze et al., 2003; Wirshing et al., 1999). Increases in body weight accompany a substantial risk of type II diabetes (Gonçalves, Araújo, & Martel, 2015; Tschoner et al., 2009). Second, many atypical antipsychotic drugs produce a cardiovascular effect called **QT interval prolongation**. The QT interval refers to readings found on an electrocardiogram, which is used to monitor the components of heartbeat.

**QT interval prolongation** Prolonged heartbeat interval found on an electrocardiogram

Although prolonging the QT intervals appears safe in itself, this condition can degenerate into a more serious condition called *torsades de pointes*, which may lead to cardiac arrest (Ray, Chung, Murray, Hall, & Stein, 2009; Stollberger, Huber, & Finsterer, 2005).

Third, some atypical antipsychotic drugs pose a slight risk of producing **agranulocytosis**, a disorder characterized by reduced white blood cell counts in the immune system. Clozapine is most noted for this adverse effect. As a result, patients prescribed clozapine must have weekly or monthly blood draws to monitor white blood cell counts (Amsler, Teerenhovi, Barth, Harjula, & Vuopio, 1977).

**Agranulocytosis** Disorder characterized by reduced white blood cell counts in the immune system

As noted for the typical antipsychotic drugs, we also find atypical antipsychotic drugs used as antiemetics. In fact, concerns over side effects found for the typical antipsychotic drugs tend to make atypical antipsychotic drugs preferred for antiemetic effects if effective. Olanzapine, in particular, is used as an effective antiemetic, which is likely due to its antagonist actions at $D_2$ and 5-$HT_3$ receptors (Jordan et al., 2014).

## STOP & CHECK

1. We characterize _____ antipsychotic drugs as having an efficacy for both positive and negative symptoms, as well as cognitive impairment.
2. Clozapine and potentially other atypical antipsychotic drugs carry a risk of _____, a condition noted by reduced white blood cell counts.

1. atypical 2. agranulocytosis

## Pharmacological Actions of Atypical Antipsychotic Drugs

As noted earlier, the principal mechanism of action for typical antipsychotic drugs consists of dopamine $D_2$ receptor blockade. We find more complex mechanisms of actions in atypical antipsychotic drugs. These mechanisms fall largely into two hypotheses for atypical antipsychotic drugs.

The first hypothesis, referred to as the **serotonin-dopamine (or 5-$HT_{2A}$-$D_2$ receptor) hypothesis**, states that atypical antipsychotic drug effects derive from preferential antagonism of serotonin$_{2A}$ (5-$HT_{2A}$) receptors compared to dopamine $D_2$ receptors. As shown in **Table 15.3**, receptor binding studies support this hypothesis by finding that the vast majority of atypical antipsychotic drugs fit this profile (Meltzer, Matsubara, & Lee, 1989; Schotte et al., 1996). Note that for the atypical antipsychotic drugs shown, greater affinities, expressed as $K_i$'s, occur for the 5-$HT_{2A}$ receptor compared to the $D_2$ receptor.

**Serotonin-dopamine (or 5-$HT_{2A}$-$D_2$ receptor) hypothesis** Hypothesis stating that atypical antipsychotic drug effects derive from preferential antagonism of serotonin 5-$HT_{2A}$ receptors compared to dopamine $D_2$ receptors

**Fast $D_2$-off** Hypothesis stating that atypical antipsychotic effects derive from a rapid dissociation of the antipsychotic drug from the $D_2$ receptor

The second hypothesis, referred to as the **fast $D_2$-off** hypothesis, states that atypical antipsychotic effects derive from a rapid dissociation of the antipsychotic drug from the $D_2$ receptor. Typical antipsychotic drugs, on the other hand, slowly dissociate from the $D_2$ receptor (Kapur & Seeman, 2000). In other words,

**TABLE 15.3 Receptor Binding Affinities for Haloperidol and Clozapine**

| Receptor | Haloperidol | Clozapine |
|---|---|---|
| $D_2$ | 1.4 | 150 |
| Serotonin $(5\text{-HT})_{2A}$ | 25 | 3.3 |
| $5\text{-HT}_{2C}$ | >5,000 | 13 |
| Muscarinic cholinergic receptors ($M_1$–$M_5$) | 4,670 | 34 |
| $\alpha_1$ adrenoceptors | 19 | 23 |
| $\alpha_2$ adrenoceptors | >5,000 | 160 |

*Source:* Data from Schotte et al. (1996).

*Note:* The numbers in the table represent the binding affinity ($K_i$ values in nM) of haloperidol and clozapine for certain receptors in the brain. The lower the number on the table, the greater the binding affinity (i.e., the greater strength of binding) the drug has for the receptor. For example, haloperidol has a greater affinity for the $D_2$ receptor than it does for the $5\text{-HT}_{2A}$ receptor, whereas the opposite is true for clozapine. Clozapine has a greater affinity for muscarinic receptors and for noradrenergic $\alpha_2$ adrenoceptors than haloperidol does, and both drugs have a similar affinity for the $\alpha_1$ adrenoceptor.

atypical antipsychotic drugs do not block $D_2$ receptors for as long a time as typical antipsychotic drugs. While we find support for both hypotheses, at present we find pharmaceutical companies most often following the $5\text{-HT}_{2A}$-$D_2$ receptor hypothesis for developing new atypical antipsychotic drugs (Carpenter & Davis, 2012).

### *Pharmacological Effects Generated From Other Receptor Actions*

As shown in Table 15.3, antipsychotic drugs bind to more than dopamine and serotonin receptors. Although the primary hypotheses for antipsychotic drugs concern the role of dopamine and serotonin receptors, other receptors may contribute to either antipsychotic effects or side effects. The $\alpha_2$ adrenoceptor for norepinephrine, for example, provides an important example of other receptor actions contributing to antipsychotic efficacy. In a preclinical study by Hertel, Fagerquist, and Svensson (1999), combined administration of an $\alpha_2$ adrenoceptor antagonist with a dopamine $D_2$ receptor antagonist led to atypical antipsychotic drug-like effects on conditioned avoidance responding without producing catalepsy (see **Box 15.2**). Thus, for atypical antipsychotic drugs, such as clozapine, which block $\alpha_2$ adrenoceptors, $\alpha_2$ adrenoceptor antagonism may contribute to atypical antipsychotic drug effects (see **Table 15.4**).

# BOX 15.2

## ANIMAL MODELS FOR IDENTIFYING TYPICAL AND ATYPICAL ANTIPSYCHOTIC DRUGS: CONDITIONED AVOIDANCE AND CATALEPSY

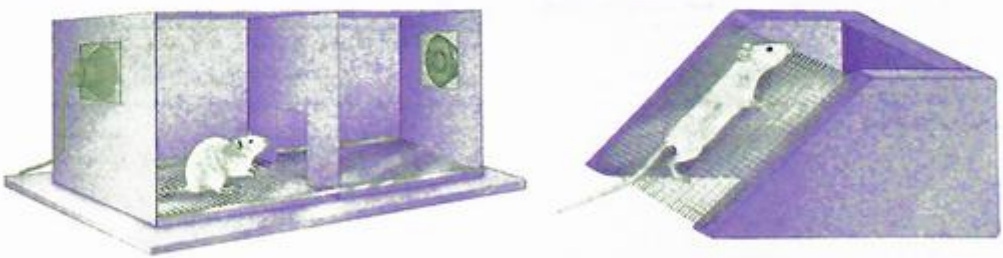
As noted previously, researchers find difficulty in identifying treatments in animals for uniquely human disorders. For finding treatments for schizophrenia, researchers tend to avoid modeling the entire disorder, but instead model some distinct feature of the disorder. Another strategy involves characterizing the distinct changes in animal behavior, whatever they may be, after administration of clinically proven antipsychotic drugs. After identifying these behaviors, we then screen experimental compounds by determining if they elicit similar behaviors. From these perspectives on antipsychotic drug development, we find two procedures highly effective for screening atypical antipsychotic drugs: conditioned avoidance responding and catalepsy.

*Conditioned avoidance responding* consists of a learning model that requires animals, usually rats or mice, to associate a warning stimulus with an impending aversive stimulus such as mild electric shock. An animal then learns to avoid the aversive stimulus by emitting some type of response, such as pressing a lever or crossing into a different compartment (**Box 15.2 Figure 1**). All known clinically effective typical and atypical antipsychotic drugs inhibit conditioned avoidance responding. Thus, antipsychotic effects manifest as poor avoidance of aversive stimulation.

Because the conditioned avoidance procedure fails to separate typical from atypical antipsychotic drugs, we add an assessment of *catalepsy* in these experiments. Catalepsy assessments consist of recording how long an animal remains in a certain posture. As presented in this chapter, typical—but not atypical—antipsychotic drugs produce EPS at therapeutically effective doses. By using catalepsy as an index of EPS in animals, researchers can determine if EPS occurs at doses effective in reducing accuracy in the conditioned avoidance response task.

**BOX 15.2 FIGURE 1** **Conditioned Avoidance Response Task**

During a conditioned avoidance response task, an organism learns to emit an avoidance response upon the activation of a warning stimulus (left). Failure to emit an avoidance response will result in the organism receiving an aversive stimulus, such as an electric shock. We can measure catalepsy in rodents using an inclined grid (right) where researchers record the amount of time taken for a rodent to move on the grid. Cataleptic rats or mice tend to take on a frozen posture on the grid. Other catalepsy models also examine lack of movement as an index of catalepsy.



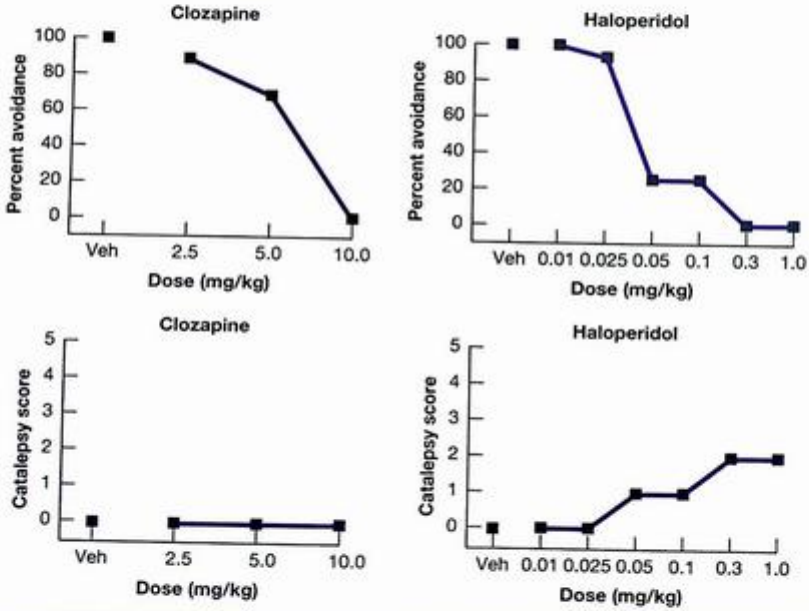
*(Continued)*

(Continued)

For example, Holly, Ebrecht, and Prus (2011) evaluated the atypical antipsychotic drug clozapine and the typical antipsychotic drug haloperidol using these two procedures. As shown in **Box 15.2 Figure 2**, both clozapine and haloperidol led to significant decreases in avoidance of the aversive stimulation. Haloperidol, however, produced these decreases in avoidance at doses that significantly increased catalepsy, whereas clozapine produced no effects on catalepsy. By putting these findings together, clozapine produces antipsychotic effects without producing EPS, a key feature of atypical antipsychotic effects.

## BOX 15.2 FIGURE 2 Antipsychotic Effects in the Conditioned Avoidance Response Task

Both the atypical antipsychotic drug clozapine (left) and the typical antipsychotic drug haloperidol (right) decrease the percentage of trials a laboratory rat avoided mild aversive stimulation (top panels). Haloperidol, but not clozapine, increased scores divided in time increments during a catalepsy assessment (bottom panels). The *x*-axis for all graphs shows the dose of each drug expressed in mg/kg.




*Source:* Holly et al. (2011).

**TABLE 15.4 Receptors and Antipsychotic Effects**

| Receptor (Neurotransmitter) | Antipsychotic Receptor Action | Effects |
|---|---|---|
| $\alpha_2$ adrenoceptor (norepinephrine) | Antagonism | May contribute to atypical antipsychotic effects when combined with $D_2$ receptor antagonism |
| $D_2$ receptor (dopamine) | Antagonism | Antipsychotic effects; EPS |
| $H_1$ receptor (histamine) | Antagonism | Drowsiness; weight gain and risk of type II diabetes |
| Muscarinic receptor (acetylcholine) | Antagonism | Dry eyes, dry mouth, and other anticholinergic effects |
| 5-$HT_{2A}$ receptors | Antagonism | Atypical antipsychotic effects when combined with $D_2$ receptor antagonism |
| 5-$HT_{2C}$ receptors | Antagonism | Weight gain and risk of type II diabetes |

For some atypical antipsychotic drugs, muscarinic receptor antagonism causes dry eyes, dry mouth, and other anticholinergic effects. Clozapine's antagonism of histamine $H_1$ receptors causes drowsiness, similar to how an antihistamine causes drowsiness, during the first several days of treatment (Ahnaou, Megens, & Drinkenburg, 2003). Receptor binding studies also implicate $H_1$ receptors, as well as 5-$HT_{2C}$ receptors, in antipsychotic drug-induced weight gain and subsequent risk of type II diabetes (Table 15.4; Kroeze et al., 2003; Reynolds, Hill, & Kirk, 2006).

## Third-Generation Antipsychotic Drugs

**Third-generation antipsychotic drugs** produce antipsychotic effects through a mechanism(s) of action different from those of typical and atypical antipsychotic drugs. In particular, potential third-generation antipsychotic drugs have deviated from the pharmacological actions found among typical and atypical antipsychotic drugs, rather than having unique therapeutic effects. Currently, the only clinically available compound that might qualify as a third-generation antipsychotic drug is *aripiprazole (Abilify)*.

**Third-generation antipsychotic drugs**
Drugs that produce antipsychotic effects through a mechanism(s) of action different from those of typical and atypical antipsychotic drugs

Unlike typical and atypical antipsychotic drugs, aripiprazole functions as a weak partial agonist for dopamine $D_2$ receptors at therapeutic doses. Yet, aripiprazole shares antagonist effects at 5-$HT_{2A}$ receptors, making this drug somewhat similar

to atypical antipsychotic drugs (Burris et al., 2002). Clinically, aripiprazole exhibits atypical antipsychotic effects because it is unlikely to produce EPS at therapeutically effective dosages. Aripiprazole appears slightly less effective than the atypical antipsychotic drug olanzapine for treating schizophrenia, but might offer less risk of type II diabetes (Fleischhacker et al., 2009).

## Administration Forms for Antipsychotic Drugs

Pharmaceutical companies provide all typical and atypical antipsychotic drugs in pill form, allowing for oral administration. However, patient compliance considerations lead companies to develop other administration routes as well. In a hospital, patients, out of possible mistrust of health care staff, may refuse to take a medication or attempt to hide medication under their tongues. During in-patient care, patients may receive intramuscular injections of antipsychotic drugs instead. Drug developers have sought to provide antipsychotic drugs in dissolvable pill or nasal spray form (Miller, Ashford, Archer, Rudy, & Wermeling, 2008; Potkin, Cohen, & Panagides, 2007). We also find many antipsychotic drugs available in *depot* administration forms. **Antipsychotic depot injections** (or **long-acting antipsychotic injections**) provide a slow release of antipsychotic drug, over the course of weeks, after a single injection. A depot administration circumvents concerns over patient compliance and provides for a steady state of drug effects.

**Antipsychotic depot injections (or long-acting antipsychotic injections)**
Drug formulation that provides a slow release of antipsychotic drug, over the course of weeks, after a single injection

Many antipsychotic drugs produce active metabolites. For example, the active metabolite of risperidone, called *paliperidone (Invega)*, was recently developed as an atypical antipsychotic drug (Dlugosz & Nasrallah, 2007). Although this is the first active metabolite approved clinically as an atypical antipsychotic drug, the active metabolite of clozapine, N-desmethylclozapine (*Pimavanserin*), has also shown promising antipsychotic effects in animal models (Lameh et al., 2007; Philibin et al., 2009).

## Pharmacogenetics and Antipsychotic Effects

We find significant variety across individuals in their physiological responses to antipsychotic drugs. The CYP2D6 and CYP2C19 enzymes metabolize approximately half of all types of antipsychotic drugs. Other P450 enzymes include CYP1A2, CYP2A6, CYP2B6, CYP3A4, CYP3A5, and CYP3A7. Polymorphisms for the enzymes cause some individuals to be poor metabolizers or rapid metabolizers of antipsychotic drugs, which may account for how practitioners adjust dosing for patients to achieve therapeutic effects or avoid adverse effects. For polymorphisms of the CYP2D6 enzyme, for example, Kirchheiner and colleagues (2004) found that dose reductions or increases among patients in clinical trials correlated with one's metabolizer status for this enzyme. While dosing changes for psychiatric medication are a regular practice, those considered a poor metabolizer or an ultrarapid metabolizer may instead benefit from changing to an antipsychotic drug metabolized by another P450 enzyme. Testing for enzymatic polymorphisms can therefore guide the selection of antipsychotic drugs.

## STOP & CHECK

1. An important pharmacological distinction between atypical and typical antipsychotic drugs is that atypical antipsychotic drugs act as an antagonist for both $D_2$ receptors and _____ receptors.
2. The _____ hypothesis states that *atypical* antipsychotic drug effects derive from a quick dissociation from the dopamine $D_2$ receptor.
3. A _____ injection of antipsychotic drug provides for a slow release of antipsychotic drug after a single injection.

1. 5-HT$_{1A}$, 2. fast D$_2$-off, 3. depot

## Antipsychotic Drugs and Autism

**Autism spectrum disorder (or autism)** Neurodevelopmental disorder consisting of social impairments; verbal and nonverbal language difficulties; irritability (e.g., emotional outbursts, tantrums); and repetitive behaviors

**Autism spectrum disorder** (often referred to as simply **autism**) is a neurodevelopmental disorder consisting of social impairments; verbal and nonverbal language difficulties; irritability (e.g., emotional outbursts, tantrums); and repetitive behaviors typically occurring before age three. The general worldwide estimate of autism is one percent (American Psychiatric Association, 2013a). Yet, we find a number of studies reporting dramatic increases in autism diagnoses. For example, the U.S. Centers for Disease Control and Prevention reported a 78 percent increase in autism diagnoses from 2002 to 2008 (Baio, 2012). A fivefold increase in autism diagnoses occurred in the United Kingdom in the 1990s, but rates plateaued in the 2000s (Taylor, Jick, & MacLaughlin, 2013). We find a four-times greater prevalence of autism in males than in females (Chakrabarti & Fombonne, 2005).

Numerous hypotheses exist for the causes of autism. Researchers and clinicians agree on genetic links to this disorder, which began with twin studies showing that autism occurring in one monozygotic twin will likely occur in the other monozygotic twin (Bailey et al., 1995; Greenberg, Hodge, Sowinski, & Nicoll, 2001). In fact, one study found that in 92 percent of cases in which a monozygotic twin received an autism diagnosis, the other twin either had autism or exhibited features related to autism (Bailey et al., 1995). Studies have mostly linked genetic abnormalities to multiple chromosomes, including four and seven (Alarcón et al., 2002; Schellenberg et al., 2006). From affected chromosomes, numerous genetic changes could lead to neurodevelopmental effects (Szatmari et al., 2007). We find general consensus relating to abnormal connectivity in the prefrontal cortex, which may have implications in a host of cognitive, social, and emotional features in this disorder (Courchesne et al., 2011; Just, Cherkassky, Keller, & Minshew, 2004). Another emerging concept is that activity in the visual system may be out of sync with activity in the motor system, perhaps leading to an individual not visually perceiving or processing the consequences of motor responses. This might account for the difficulty those with autism have for imitating gestures (Nebel et al., 2015).

The management of autism often includes *applied behavior analysis* therapy or psychoactive medications. An applied behavior analyst normally provides therapy for a child or adult with autism with the goal of correcting problem social, communicative, and adaptive behaviors. One of the primary psychoactive drug approaches involves prescribing antipsychotic drugs. Those currently approved by the U.S. FDA for use in autism include *aripiprazole* and *risperidone*.

Antipsychotics primarily manage certain features of autism. Both aripiprazole and risperidone reduce autism-related irritability and, in fact, are specifically approved by the FDA for this purpose. For example, McCracken and colleagues (2002) reported that eight weeks of risperidone treatment in children and adolescents with autism led to greater reductions in irritability than placebo in about two-thirds of their patients. Owen and colleagues (2009) later reported similar findings after eight weeks of aripiprazole treatment. Yet, these studies also demonstrated similar adverse effects as seen in those with schizophrenia, including risks of weight gain, fatigue, and EPS. In fact, the likelihood of these adverse effects occurring appears higher in children and adolescents than in adults (Correll, 2008).

## STOP & CHECK

1. Studies in monozygotic _____ first suggested a genetic cause for autism.
2. Abnormal connectivity in the _____ may contribute to many of the symptoms of autism.
3. Antipsychotic drugs are specifically approved to treat _____ in autism.

1. twins 2. prefrontal cortex 3. irritability

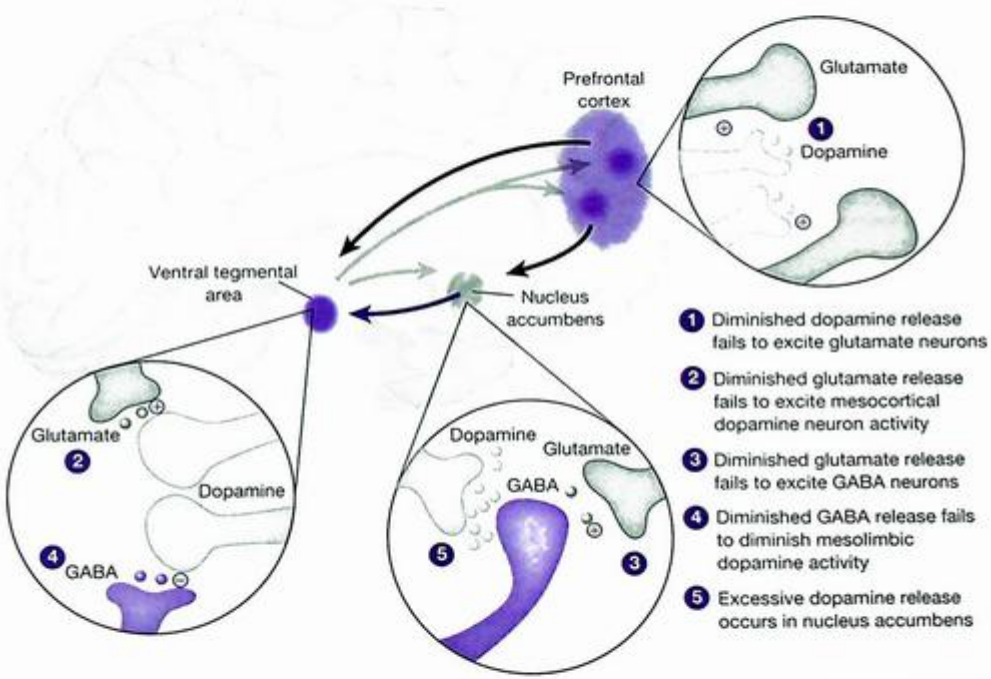
## From Actions to Effects: Antipsychotic Drug Actions and Neurotransmission in Schizophrenia

Beyond differences in receptor actions between typical and atypical antipsychotic drugs, microdialysis studies reveal important differences in dopamine neurotransmission between these drug classes. Moreover, these neurotransmission differences correspond to the role of dopamine in the glutamate hypothesis of schizophrenia. As shown in **Figure 15.8**, the glutamate hypothesis, together with other evidence, reveals diminished cortical levels of dopamine and enhanced limbic system levels of dopamine in schizophrenia. Figure 15.8 focuses on the prefrontal cortex and nucleus accumbens for these regions, respectively. Researchers relate diminished dopamine levels in the prefrontal cortex to cognitive impairment and negative symptoms. The different effects that atypical and typical antipsychotic drugs have on dopamine levels in the prefrontal cortex relate to their general clinical effects for cognitive impairment and negative symptoms.

Microdialysis studies find that atypical, but not typical, antipsychotic drugs increase dopamine concentrations in the prefrontal cortex. For example, in a study

**FIGURE 15.8** **Dopamine and Glutamate in Schizophrenia and Antipsychotic Drug Actions**

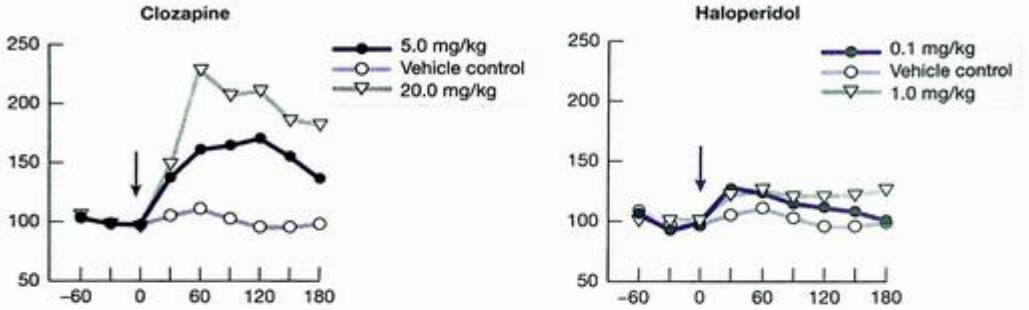
In schizophrenia, disruption in neurotransmission occurs for glutamate and dopamine. In this image, we find underactive mesocortical dopamine neurons that originate in the ventral tegmental area and terminate in prefrontal cortex and other parts of the cortex. Thus, dopamine levels in the prefrontal cortex may be too low. Diminished dopamine activity in the prefrontal cortex causes less activation of glutamate neurons that innervate the ventral tegmental area and facilitate a positive feedback loop. Lower activity of glutamate neurons from the prefrontal cortex to the nucleus accumbens may result in less activation of GABA neurons that terminate in the ventral tegmental area. Diminished GABA neuron activity may disinhibit mesolimbic dopamine neurons, leading to increased dopamine release in the nucleus accumbens and perhaps other parts of the limbic system. Thus, overall this model demonstrates how dopamine levels in the prefrontal cortex may be low, while dopamine levels in the limbic system may be high. The "+" symbols represent excitatory effects, and the "-" symbols represent inhibitory effects.




by Kuroki, Meltzer, and Ichikawa (1999), the atypical antipsychotic drugs clozapine and risperidone significantly increased dopamine concentrations in the rat medial prefrontal cortex. However, the typical antipsychotic drug haloperidol failed to increase dopamine concentrations in the prefrontal cortex (**Figure 15.9**).

## FIGURE 15.9 Antipsychotic Drugs and Dopamine Release

Microdialysis procedures reveal that atypical antipsychotic drugs such as clozapine (left) produce increased dopamine concentrations in the prefrontal cortex, although typical antipsychotic drugs such as haloperidol tend to have minimal effects on dopamine concentrations in the prefrontal cortex (right). The arrow indicates when the injection of clozapine or haloperidol was given. The *y*-axis shows the percentage of dopamine level change compared to baseline plotted at the 100 percent level. The *x*-axis shows the time before (with minus signs) and after drug injection.




*Source:* Kuroki, T., Meltzer, H. Y., & Ichikawa, J. (1999). Effects of antipsychotic drugs on extracellular dopamine levels in rat medial prefrontal cortex and nucleus accumbens. *J Pharmacol Exp Ther, 288*(2), 774–781. Used with permission.

To determine why atypical antipsychotic drugs elevated prefrontal cortical dopamine levels, Liegeois, Ichikawa, and Meltzer (2002) assessed the effects of drugs selective for 5-$HT_{2A}$ receptors and $D_2$ receptors on prefrontal cortical dopamine concentrations. They found that neither the 5-$HT_{2A}$ receptor antagonist M100907 nor haloperidol, a $D_2$ receptor antagonist, significantly increased dopamine concentrations in the prefrontal cortex. After combining the two drugs, however, these researchers found significant increases in dopamine concentrations in the prefrontal cortex. Based on these findings, the actions of atypical antipsychotic drugs on 5-$HT_{2A}$ and $D_2$ receptors may account for their effects on cortical dopamine neurotransmission and possibly their ability to improve cognitive impairment and negative symptoms in schizophrenia.

## STOP & CHECK

1. How do dopamine levels in the prefrontal cortex relate to cognitive impairment in schizophrenia?
2. How might atypical antipsychotic drugs—but not typical antipsychotic drugs—increase prefrontal cortical dopamine levels?

1. Diminished prefrontal cortical dopamine levels may lead to cognitive impairment in schizophrenia.
2. Combined actions of 5-$HT_{2A}$ and $D_2$ receptor antagonism appear to increase prefrontal cortical dopamine concentrations.

## CHAPTER SUMMARY

Schizophrenia is a severe thought disorder diagnosed by the presence of positive symptoms and negative symptoms. In addition, many patients exhibit deficits in cognitive functioning, which is an important predictor of functional outcomes. Schizophrenia occurs from genetic and environmental factors. The main treatments for schizophrenia consist of typical and atypical antipsychotic drugs. Typical antipsychotic drugs reduce positive symptoms of schizophrenia and produce extrapyramidal side effects at therapeutically effective doses. They produce antipsychotic effects by serving as antagonists for $D_2$ receptors. Atypical antipsychotic drugs are effective for positive symptoms and, to some degree, negative symptoms and cognitive impairment. They are also capable of producing these therapeutic effects at doses that do not produce EPS. The therapeutic effects of atypical antipsychotic drugs are produced through preferential antagonism of 5-$HT_{2A}$ receptors compared to $D_2$ receptors or they are produced by quicker dissociation from $D_2$ receptors. In either case, an important factor in the clinical effects of atypical antipsychotic drugs may be their ability to enhance dopamine levels in the prefrontal cortex while reducing dopamine levels in the limbic system. Many antipsychotic drugs produce significant weight gain and subsequently carry the risk of type II diabetes. For the management of autism spectrum disorder, antipsychotic drugs can reduce autism-related irritability.

## KEY TERMS

Schizophrenia 493
Positive symptoms 493
Negative symptoms 493
Treatment-resistant schizophrenia 494
Functional outcomes 494
Sensory-gating deficit 495
Cognitive dysmetria 496
Prodromal phase of schizophrenia 497
Neurodevelopmental hypothesis 499
Dopamine hypothesis (for schizophrenia) 503
Glutamate hypothesis (for schizophrenia) 503
Typical antipsychotic drugs (or first-generation or classical antipsychotic drugs) 506
Extrapyramidal side effects (EPS) 507
Tardive dyskinesia 507
Neuroleptic malignant syndrome (NMS) 509
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Fast $D_2$-off 511
Third-generation antipsychotic drugs 515
Antipsychotic depot injections (or long-acting antipsychotic injections) 516
Autism spectrum disorder (or autism) 517

# Glossary

**1,4-butanediol.** Industrial solvent that produces GBL in the body; GBL subsequently transforms into GHB

**18th Amendment.** Amendment to U.S. Constitution that banned the sale and distribution of alcohol

**21st Amendment.** Repealed the 18th Amendment

**Absorption.** Passage of a drug from the site of administration to the bloodstream

**Accelerated time.** Perceived faster passage of time associated with cannabis use

**Acetaldehyde.** Metabolite produced from enzymatic conversion of alcohol with alcohol dehydrogenase

**Acetylcholinesterase.** Enzyme that catabolizes, or breaks down, acetylcholine

**Action potential.** Rapid depolarization, causing the charge in the neuron to become temporarily positive

**Active metabolite.** A drug's metabolite that has physiological effects

**Active transport through the blood–brain barrier.** Mechanisms consisting of channels or other types of proteins that transport chemicals through endothelial cell membranes

**Acute tolerance.** Decreased responsiveness to a drug's effects after a single administration of the drug

**Acute tolerance to alcohol.** Tolerance that occurs when alcohol's behavioral effects are weaker for declining BACs than for inclining BACs

**Additive drug effects.** The magnitude of the combined drug effect is the sum of each drug's effect alone

**Add-on treatment.** The administration of a medication to adjust the effects of another medication; often used to describe a drug boosting the therapeutic effects of a medication

**Adenosine.** A neuromodular that has inhibitory effects on neurons throughout the central and peripheral nervous system

**Agonist.** Drug that activates a neurotransmitter receptor

**Agoraphobia.** Anxiety about being in situations from which escape is difficult or embarrassing

**Agranulocytosis.** Disorder characterized by reduced white blood cell counts in the immune system

**Alcohol dehydrogenase.** Enzyme that metabolizes alcohol

**Alcohol myopia.** Alcohol-induced state of narrowed attention, perceptions, and thoughts to cues, emotional states, or specific sets of information

**Alcohol poisoning.** Alcohol-induced inhibition of autonomic system functions, including breathing, heart functioning, and the gag reflex

**Alcohol priming.** Tendency of users to develop an urge to consume more alcohol after having one or two drinks of alcohol

**Alcohol stupor (or drunken stupor).** Dulled senses and poor cognitive functioning caused by overconsumption of alcohol; also known as drunken stupor

**Alcohol withdrawal syndrome (delirium tremens).** Alcohol withdrawal syndrome characterized by hallucinations, trembling, confusion, disorientation, and agitation

**Alcoholic cardiomyopathy.** Low cardiac output from enlargement of the heart and dilation of heart chambers caused by heavy and chronic alcohol use

**Alcoholic fatty liver disease.** Fat accumulation in the liver due to regular alcohol consumption

**Alcoholics Anonymous.** A 12-step program for alcohol addiction that provides extensive social support to encourage drinking abstinence for its anonymous members

**Alkaloid.** Plant-derived physiologically active organic compounds that contain nitrogen

**All-or-none law.** Magnitude of an action potential is independent from the magnitude of potential change that elicited the action potential

**Allostasis.** The maintenance of a physiological state around a setpoint that has deviated from the body's normal setpoint

**Alzheimer's disease.** A progressive neurological disorder characterized by severe impairments in cognition, motivation, language production and comprehension, and mood regulation

**Amotivational syndrome.** Lack of motivation to engage in productive activities possibly related to cannabis use

**Amphetamines.** Class of psychostimulant drugs that share a similar structure

**Amygdala (role in drug addiction).** During chronic use of an abused substance, associates stimuli commonly present during drug use with the reinforcing effects of the drug; elicits physical withdrawal symptoms and a negative emotional state when drug is absent

**Amyl nitrite (or poppers).** An inhalant recreationally used for feelings of warmth, throbbing sensations, light-headedness, and enhanced sexual experiences

**Anorectics.** Appetite-suppressant drugs

**Antagonist.** Drug that fails to activate a receptor and prevents a neurotransmitter from activating the receptor

**Antiemetic.** Drugs that reduce nausea and vomiting

**Antipsychotic depot injections (or long-acting antipsychotic injections).** Drug formulation that provides a slow release of antipsychotic drug, over the course of weeks, after a single injection

**Anxiety.** Worry and distress concerning potential events or outcomes

**Anxiolytic drug.** Drug developed and prescribed to treat anxiety

**Area postrema.** Area in the medulla that produces vomiting

**Associative learning.** Process by which an organism learns associations between stimuli or between behaviors and stimuli

**Astrocyte.** Glial cell that plays a role in forming the blood-brain barrier, facilitating neuronal function, and responding to injury

**Attention deficit hyperactivity disorder (ADHD).** A disorder characterized by inattention, hyperactivity, and inability to control impulsive behaviors

**Atypical antidepressant drugs.** Antidepressant drugs that reduce depression through mechanisms that differ from those of other antidepressant classifications

**Atypical antipsychotic drugs (or second-generation or novel antipsychotic drugs).** Antipsychotic drugs that reduce positive and negative symptoms and carry a low risk of EPS at therapeutic doses

**Augmentation strategy (or adjunctive treatment/therapy).** Administration of a drug intended to boost the therapeutic effects of a medication

**Autism spectrum disorder (or autism).** Neurodevelopmental disorder consisting of social impairments; verbal and nonverbal language difficulties; irritability (e.g., emotional outbursts, tantrums); and repetitive behaviors

**Autonomic nervous system.** System that controls involuntary movements for vital functions, such as heartbeat, breathing, swallowing, and digestion

**Autoreceptor.** Presynaptic receptor that is activated by neurotransmitters released from the same axon terminal

**Axons.** Part of a neuron that releases neurotransmitters for signaling with other neurons

**Bad trip.** Disturbing true hallucinations, psychotic episodes, negative emotional states, altered perceptions of time, and out-of-body sensations

**Barbiturate abstinence syndrome.** Anxiety, muscle weakness, and abdominal pain caused by abrupt cessation of barbiturate use

**Basal ganglia.** Forebrain structure that aids in the stabilization of movement

**Beer.** An alcoholic beverage, usually with five percent or less alcohol content, made through fermentation from certain starches such as barley, wheat, or rice

**Behavioral tolerance.** Decreased behavioral responsiveness to a drug's effects

**Behavioral tolerance to alcohol.** Reduced behavioral impairment to alcohol

**Benzodiazepine withdrawal syndrome.** A condition caused by abrupt cessation of a chronically used benzodiazepine characterized by anxiety, mania, suicidality, and convulsions

**Beta blocker (or beta receptor antagonist).** Drug that inhibits the fight-or-flight response by blocking beta receptors for norepinephrine and epinephrine

**Binding affinity.** Drug's strength of binding to a receptor

**Binge drinking.** Consumption of at least five standard drinks for men and four standard drinks for women during one occasion

**Bioavailability.** Ability of a drug to reach a site of action

**Biotransformation (or metabolism).** Process of converting a drug into one or more metabolites

**Bipolar disorder.** Mental disorder characterized by abnormal changes between depressive and manic mood states

**Black box warning (or boxed warning).** A warning on a drug's package insert given a black border around it to draw special attention to it

**Blackout.** Term used to describe anterograde amnesia due to alcohol use

**Blood alcohol concentration (BAC).** Number of grams of alcohol in a 100 ml volume of blood

**Blood–brain barrier.** Barrier that surrounds the blood capillaries and vessels in the brain and prevents substances in the blood from entering the brain

**Brand name (or trade name).** A trademarked name a company provides for a drug

**BZ I site.** Allosteric site on the $GABA_A$ receptor $\alpha_1$ subunit that a benzodiazepine can bind to; also referred to as the high-affinity site

**BZ II site.** Allosteric site on the $GABA_A$ receptor $\alpha_2$, $\alpha_3$, or $\alpha_5$ subunit that a benzodiazepine can bind to; also referred to as the low-affinity site

**C-1021T polymorphism.** Polymorphism that causes low expression of dopamine β-hydroxylase, the enzyme that converts dopamine to norepinephrine

**Caffeinated alcoholic beverage.** Beverage made by mixing energy drinks with alcohol

**Caffeine.** Psychostimulant compound and a member of the xanthine chemical class

**Caffeinism.** Condition characterized by agitation, anxiety, insomnia, and negative mood as well as rapid heart rate and high blood pressure

**Cannabinoid receptors.** G-protein-coupled receptors consisting of $CB_1$ and $CB_2$ activated by cannabinoids

**Cannabinoids.** Substances that act on cannabinoid receptors

**Cannabis.** Three varieties of plants that contain naturally occurring psychoactive cannabinoids

**Cannabis use disorder.** Defined by the DSM-5 as cannabis use meeting the criteria for a substance use disorder

**Cannabis withdrawal syndrome.** Occurrence of physical and psychological withdrawal symptoms in the absence of cannabis

**Catabolism.** Process involving the enzymatic breakdown of neurotransmitters and other molecules

**Catechol-O-methyltransferase (COMT).** Enzyme that breaks down dopamine and norepinephrine

**Cathinone.** Psychostimulant derived from the leaves of *Catha edulis*

**Cerebellum.** A hindbrain structure that facilitates balance and the timing of movements

**Cerebral blood flow.** Blood flow throughout the brain

**Cerebral cortex.** The surface of the brain; comprising gyri and sulci

**Cerebrospinal fluid.** Fluid that surrounds cells in the brain

**Certain Safety Index.** A therapeutic index calculated by dividing a $TD_1$ by an $ED_{99}$

**Cheese reaction.** Overactivated sympathetic nervous system functioning because of MAO inhibition that leads to increased heart rate, hypertension, sweating, and inhibited digestion

**Chemical aversion therapy (or emetic therapy).** Attempt to eliminate alcohol use by associating emesis (i.e., vomiting) with alcohol

**Chemical name.** A name that details a drug's chemical structure

**Chemoreceptor trigger zone.** Area in the medulla unprotected by the blood–brain barrier receptive to substances in the blood or cerebrospinal fluid that, when activated, sends inputs to the area postrema to produce vomiting

**Chippers.** Smokers who fail to develop an addiction to tobacco

**Cholinergic neurons.** Neurons that synthesize and release acetylcholine

**Cigar.** Tightly rolled bundle of dried tobacco leaves wrapped in a leaf

**Cigarette.** A tobacco blend rolled in a thin sheet of paper

**Cirrhosis.** A chronic liver disease characterized by poor liver functioning due to tissue scarring and diminished blood flow, affecting nutrient metabolism, protein synthesis, and other vital processes

**Clinical study reports.** Detailed summaries of a clinical study's design and results

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

**Coca paste.** Liquid paste made from the breaking and mixing of coca leaves

**Cocaine.** Psychostimulant derived from the leaves of *erythroxylon coca*

**Cocaine- and amphetamine-regulated transcript (CART).** Peptide neurotransmitter produced after psychostimulant administration

**Cognitive dysmetria.** Abnormalities in processing, coordinating, and responding to information

**Cognitive-behavioral therapies.** Therapies that teach drug-addicted individuals to identify and reduce urges to use a substance

**Cognitive-behavioral therapies for alcohol dependence.** Therapies that seek to improve an individual's cognitive and behavioral skills toward changing problem alcohol use

**Cognitive-enhancing drugs (or smart drugs or nootropics).** Improves concentration, memory, or other cognitive functions

**Combination drug strategy.** The administration of a medication to adjust the effects of another medication

**Competitive antagonist.** Drug that binds to the same site as a neurotransmitter, preventing a neurotransmitter from binding to the receptor

**Conditioned (or contingent) tolerance.** Stimuli associated with substance use elicit compensatory actions that reduce a drug's effects

**Conditioned stimulus.** A stimulus that acquires the behavioral controlling properties of another stimulus that is involved in an associated learning process

**Construct validity.** How well a study's findings relate to the underlying theory of a study's objectives

**Contact high.** Positive subjective effects from secondhand exposure to cannabis smoke

**Controlled Substances Act.** U.S. federal law passed in 1970 that regulates sale and possession of drugs identified as controlled substances

**Controlled substances schedules.** A scheduling system mandated by the Controlled Substances Act that classifies a drug according to its drug abuse potential and medical use potential

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

**Cortisol.** Hormone released from the adrenal gland during stress

**Cotinine.** Active metabolite of nicotine

**Craving.** A strong urge to use a drug

**Cross tolerance.** Tolerance for other drugs with similar biological actions

**Dabbing.** Inhaling vapors emitted from a flame-heated hashish oil and butane mixture (the "dab") that was dabbed onto the end of a glass or titanium rod

**Default mode network.** Activity occurring in a series of brain structures during times of non-goal-directed activity or inattention

**$\Delta^9$-tetrahydrocannabinol ($\Delta^9$-THC).** Key psychoactive substance in cannabis

**Dendrites.** Parts of a neuron that receive information from other neurons

**Dependent variable.** A study variable measured by a researcher

**Depolarization.** Reduced difference between the positive and negative charges on each side of a membrane

**Depressant.** A drug or substance that diminishes physiological activity and cortical arousal

**Detoxification.** Process aimed at ceasing drug intoxication and reducing withdrawal symptoms

**Detoxification (or detoxication).** Process that uses an opioid agonist or antagonist to reduce withdrawal symptoms

**Dextromethorphan.** Opioid receptor drug used in cough suppressant that in large-enough doses can produce psychedelic effects

**Dimethyltryptamine (DMT).** Hallucinogenic compound found in certain South American plants and produced endogenously

**Discriminative stimulus.** A stimulus that, when present, signals the availability of reinforcement

**Disease model.** Model that characterizes drug addiction as a disease

**Disinhibition.** Weakening of behavioral control

**Dissociative anesthetics.** Sedative pain-relieving drugs that produce feelings of disconnectedness from the body and have depressant and stimulant effects

**Distilled alcoholic beverages.** Alcoholic beverages produced through distillation that have a higher alcohol content than beer and wine

**Distribution.** The passage of a drug from the bloodstream to sites in the body

**Divided attention.** Sustained attention on a stimulus despite the presence of distracters

**Dopamine hypothesis (for schizophrenia).** Hypothesis for schizophrenia stating that positive symptoms arise from excessive dopamine release in the limbic system

**Dorsolateral prefrontal cortex.** Integrates sensory information received from other cortical areas and mediates working memory, planning, organizing, and other upper-level cognitive activities; important for impulse control

**Dose.** Ratio of the amount of drug per an organism's body weight

**Dose-effect curve.** Depicts the magnitude of a drug effect by dose

**Double-blind procedure.** When neither participants nor investigators know the treatment assignments during a study

**Drive theory of drug addiction.** Repeated drug use that causes a motivation, or drive, to engage in seeking a drug's positive reinforcing effects

**Drug.** An administered substance that alters physiological functioning

**Drug misuse.** Recreationally using a drug that has accepted instrumental uses

**Drug replacement therapy.** Exchanging the addictive drug with a similar but less harmful drug

**E-cigarettes (or electronic nicotine delivery systems).** Electronic nicotine vaporizers often shaped like cigarettes

**$ED_{50}$.** Value that represents the dose at which 50 percent of an effect was observed

**Effector enzymes.** Enzyme that produces second messenger proteins

**Ego dissolution.** A compromised sense of self during a psychedelic experience

**Electrical potential.** Difference between the electrical charge within a neuron versus the electrical charge of the environment immediately outside the neuron

**Elimination.** Process for how a drug leaves the body

**Elimination rate.** Amount of drug eliminated from the body over time

**Emotional blunting (or affective blunting).** Feelings of emotional detachment along with experiencing reduced positive and negative emotions

**Empathogen.** "Enhanced empathy," usually in reference to mixed stimulant–psychedelic drugs

**Emphysema.** Type of chronic obstructive pulmonary disease caused by irreversible lung damage

**En bloc blackout.** A total inability to recall events during a set period of time of alcohol intoxication

**Endocannabinoids.** Endogenous neurotransmitters, including anandamide and 2-AG, that activate cannabinoid receptors

**Endozepines.** Endogenous substances that bind to benzodiazepine sites

**Entactogen.** "Touching within," usually in reference to mixed stimulant–psychedelic drugs

**Enteric nervous system.** Subsystem of the autonomic system that controls digestion via communication within its system and with the central nervous system

**Ephedra (or ma huang).** An extract of the plant *Ephedra sinica* that contains ephedrine and pseudoephedrine

**Epigenetics.** Mechanisms of gene expression not involving alterations to DNA sequences

**Essential amino acid.** Amino acid that is not produced in the body and must come from diet

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

**Ethyl alcohol (or ethanol).** An alcohol that functions as a central nervous system depressant

**Exocytosis.** Fusing of synaptic vesicles to the axon membrane and release of stored neurotransmitters into the synaptic cleft

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

**External validity.** Refers to how well study findings generalize beyond the study conditions

**Extrapyramidal side effects (EPS).** Adverse effects consisting of tremor, muscle rigidity, and involuntary movements associated with antipsychotic drugs

**Extreme drinking.** Consuming two to three times more alcohol than in binge drinking

**Face validity.** Appearance of a test measuring what a researcher considers it to measure

**Fast $D_2$-off.** Hypothesis stating that atypical antipsychotic effects derive from a rapid dissociation of the antipsychotic drug from the $D_2$ receptor

**Fear.** A negative emotion caused by a real or perceived imminent danger or threat

**Fermentation.** Alcohol production using yeast cells and some type of starch such as grains or fruit

**Fetal alcohol syndrome.** Disorder characterized by physical and neurological abnormal development

**Fibromyalgia syndrome.** A musculoskeletal disorder characterized by widespread pain occurring as muscle tenderness as well as other symptoms including fatigue, disrupted sleep, and depressed mood

**Firing rate.** The number of action potentials occurring per unit of time, usually in milliseconds

**First-order kinetics.** The elimination of a drug in half-lives

**First-pass metabolism (or first-pass effect).** Drug metabolism that occurs prior to circulation to the body

**Flashback.** Random, short, and non-distressing memory of a previous hallucinogenic experience

**Flue curing.** Venting heat through a metal flue onto tobacco leaves

**Formication.** A tactile hallucination described as feeling like insects or worms crawling under the skin

**Fragmentary blackout (or brownout).** Incomplete memories from a period of alcohol intoxication

**Freebase.** A base form of a compound converted from a salt form of the compound

**Frontal lobe.** Region of the cerebral cortex important for decision making and movement

**Functional antagonism.** An indirect or atypical means of inhibiting a receptor's activity, such as when the net effects of a receptor agonist consist of a longer inactivated receptor state and a shorter activated receptor state

**Functional outcomes.** A patient's inclusion into a community, behaving normally in social situations, and successfully employing psychosocial skills

**G protein.** A three-subunit protein that carries out effects of a metabotropic receptor

**GABA.** Inhibitory amino acid neurotransmitter

**$GABA_A$ receptor.** Ionotropic receptor composed of five subunits and activated by the neurotransmitter GABA

**Gamma-butyrolactone (GBL).** Chemical used in household products that is converted by enzymes to GHB in the body

**Gamma-hydroxybutyrate (GHB).** Substance that serves as both a drug and a neurotransmitter that produces CNS depressant effects

**Gene.** Segment of DNA encoded with the traits expressed in an organism

**General adaptation syndrome.** Stress syndrome occurring in three progressive phases: alarm stage, resistance, and exhaustion

**Generalized anxiety disorder.** Chronic, excessive worry about events, individuals, or activities

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

**GHB withdrawal.** Withdrawal symptoms occurring within hours of last using GHB that include tremor, seizures, memory loss, anxiety, and confusion

**Glial cells (or glia cells).** Cells that support the function of neurons

**Glutamate.** Excitatory amino acid neurotransmitter

**Glutamate hypothesis (for schizophrenia).** Hypothesis for schizophrenia stating that diminished levels of glutamate release throughout the cerebral cortex and limbic system may lead to the symptoms of schizophrenia

**Glycogen synthase kinase 3 (GSK-3).** Protein kinase that promotes apoptosis and regulates inflammation

**Goal-directed behavior.** Behavior that occurs when an organism engages in learned behaviors in order to achieve a desired goal

**Good trip.** Highly pleasant sensory distortions and pseudo-hallucinations

**G-protein-coupled inwardly rectifying K+ channel (GIRK).** A $K^+$ channel that causes the influx of $K^+$ when a neuron is hyperpolarized and less $K^+$ influx when a neuron is depolarized

**Half-life.** Duration of time necessary for the body to eliminate half of a drug

**Hallucinogen persisting perception disorder.** Recurring, lengthy, and unpleasant memory from a previous hallucinogenic experience

**Hallucinogens.** Large class of psychedelic drugs that produces hallucinations as its main pharmacological effect

**Hangover.** Unpleasant experience that may occur after alcohol consumption

**Harrison Narcotics Act.** U.S. federal law passed in 1915 that restricted the sale of narcotics

**Harvard Psilocybin Project.** Studies led by Timothy Leary and Richard Alpert to examine effects of psilocybin in human volunteers

**Hashish.** Condensed preparation of cannabis that primarily contains the trichome resins from the plant

**Heteroceptor.** Presynaptic receptor that is activated by neurotransmitters different from those released from the axon terminal

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

**Hippocampus.** A forebrain structure in the limbic system important for long-term memory

**Hofmann, Albert.** Swiss chemist who discovered LSD

**Holiday heart syndrome.** Cardiac arrhythmias occurring after an acute heavy drinking episode

**Hookah.** An ornately shaped and decorated water pipe assembly consisting of a charcoal-heated, tobacco-holding chamber pipe connected through the water jar mouth and into the water, with tubes from the jar allowing for tobacco smoke inhalation

**Hormesis.** Beneficial effects produced by low doses of a toxic substance

**Hormones.** Signalling molecules derived from cholesterol and released from glands

**Hyperpolarization.** Increased difference between the positive and negative charges on each side of a membrane

**Hyperprolactinemia.** Disorder characterized by abnormally high blood levels of prolactin over prolonged periods of time, resulting in reduced lactation, loss of libido, disruptions in menstrual cycles, erectile dysfunction, and hypogonadism

**Hypersuggestibility.** A state of easy influence by suggestions that can jeopardize reality testing

**Hypothalamic–pituitary–adrenal (HPA) axis.** A system involved in physiological responses to stress

**Hypothalamus.** Structure found in the forebrain that maintains important physiological conditions, in part by motivating an organism's behavior

**Hypothalamus (role in drug withdrawal).** Elicits autonomic system effects associated with physiological withdrawal symptoms

**Impulsivity.** Decision making without reflecting adequately on the consequences of those decisions

**Incentive salience.** Attribution of salient motivational value to otherwise neutral stimuli

**Incentive-salience model.** Drug addiction that occurs after a shift from "liking" the effects of a drug to "wanting" the effects

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

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

**Inhalant overdose.** Overdose from inhalant use characterized by a series of adverse effects that can include stupor, seizure, unconsciousness, cessation of breathing, and cardiac arrest

**Inhalants.** Vaporous chemicals that elicit psychoactive effects

**Instrumental drug use.** Using a drug to address a specific purpose

**Internal validity.** Control of variables with potential to influence a dependent variable

**Interneuron.** Neuron with the soma and axon found within the same structure

**Intoxication.** A drug's effects after acute administration that overall produce an abnormal and impaired state

**Ion channels.** Pores in a neuronal membrane that allow the passage of ions

**Ionotropic receptor.** Ion channel that opens when a matching neurotransmitter binds to a site on the channel

**Irreversible MAO inhibitors.** Antidepressant drugs that irreversibly inhibit MAO

**Ketamine.** Recreationally used dissociative anesthetic that is used as an anesthetic for animals

**Kindling.** An increased seizure risk from repeated withdrawals from alcohol

**Latent inhibition.** A resistant or slower conditioning process that occurs from using a familiar stimulus in an associative learning process

**Laudanum.** An opium-containing drink intended for medical purposes

**Liberation.** Process of drug molecules separating from the pill or solution in which they were delivered

**Ligand.** A molecule that binds to a protein

**Limbic system.** Series of structures that together appear to form a ring around the thalamus and hypothalamus

**Liquid incense (or cannabinoid-enhanced electronic liquid).** Vapors emitting from a synthetic cannabinoid liquid using an e-cigarette

**Lithium.** Mood stabilizer used for treating bipolar disorder

**Long-term opioid detoxification.** Detoxification process that lasts approximately 180 days and occurs by prescribing an opioid receptor agonist or a partial opioid receptor agonist to replace the illicit opioid drug

**Long-term potentiation.** Form of synaptic plasticity important for learning and memory

**Lysergic acid diethylamide (LSD).** A representative hallucinogenic drug

**Major depressive disorder.** Disorder characterized by at least five depressive symptoms that last two weeks or longer

**Mania.** Consists of an abnormal elevation or irritation in mood along with increased arousal or energy levels

**MAO inhibitors.** Produce antidepressant effects by binding to MAO and preventing it from breaking down monoamine neurotransmitters

**Marijuana (or marihuana).** Consists of dried cannabis flowers, leaves, and stems compressed and rolled for smoking

**MDMA.** A mixed stimulant–psychedelic drug

**Medicinal cannabis.** Cannabis used for treating medical conditions such as cancer, weight gain, pain, intraocular pressure, and autoimmune diseases

**Medulla.** Structure that controls the autonomic nervous system and is situated where the spinal cord meets the hindbrain

**Melatonin.** Sleep-inducing hormone that plays an important role in circadian rhythm, our natural sleep cycle

**Mental disorder.** Impairment in normal behavioral, cognitive, or emotional functioning

**Mesocortical dopamine pathway.** Set of dopamine neurons with somas in the ventral tegmental area and axons terminating in the cerebral cortex, particularly the prefrontal cortex

**Mesolimbic dopamine pathway.** Dopamine neurons with somas in the ventral tegmental area and axons terminating in the limbic system

**Metabolic tolerance to alcohol.** Increase in liver alcohol dehydrogenase enzymes resulting in an increased rate of alcohol metabolism

**Metabolite.** Product resulting from enzymatic transformation of a drug

**Metabotropic receptor.** Receptor physically separated from parts of the neuron where the receptor exerts its effects

**Meth mouth.** Tooth decay caused by methamphetamine use

**Methadone clinics.** Specialized clinics that prescribe and dispense methadone to patients in treatment for opioid addiction

**Methyl alcohol (or methanol).** An industrial solvent that acts as a toxin for optic nerves and can be produced during the distillation process for *moonshine*

**Methylecgonidine.** By-product of the freebase synthesis process for cocaine that is harmful to the heart, lungs, and liver

**Microglial cell.** Glial cell that removes normal cellular waste and serves as an immune cell in the central nervous system

**Miosis.** Pupil constriction that can occur after opioid administration

**Mixed opioid receptor agonist–antagonists.** Drugs that exhibit agonist actions at some opioid receptors while exhibiting antagonist actions at other opioid receptors

**Mixed stimulant–psychedelic drug.** Substance that exhibits both psychostimulant effects and hallucinations

**Modal object completion.** Perception of object boundaries inferred from incomplete representations of the object

**Models of drug addiction.** Scientific attempts to characterize and explain compulsive drug use

**Monoamine hypothesis of depression.** Hypothesis stating that a monoamine neurotransmitter deficiency causes depressive mood

**Monoamine oxidase (MAO).** Enzyme that breaks down dopamine, norepinephrine, and serotonin

**Mood stabilizer.** Drug that reduces both depressive and manic symptoms

**Motor cortex.** Part of the frontal lobe that sends movement signals to the body

**Motor neuron (or motoneuron).** Neuron that conveys motor information via axons from the central nervous system

**Multiple organ failure.** Occurs due to hyperthermia from MDMA use, resulting in seizures, muscle breakdown, kidney failure, and blood vessel blockade

**Muscimol.** Psychedelic compound in *Amanita muscaria*

**Narcolepsy.** A disorder characterized by sudden bouts of daytime heavy sleepiness

**Narcotic.** A drug with sensory-dulling effects used to describe opioids but also non-opioid substances

**Naturally occurring opioid.** Opioid found in opium

**Negative modulator.** A chemical substance that binds to an allosteric site on a receptor and decreases the ability of a neurotransmitter to bind to and/or activate the receptor

**Negative symptoms.** Reduction of normal behaviors such as reduced emotional responsiveness, social withdrawal, reduced movement, and lack of motivation in schizophrenia

**Neurodevelopmental hypothesis.** Hypothesis for schizophrenia stating that abnormal nervous system development leads to irregular neuronal signalling in the brain, resulting in the characteristics of schizophrenia

**Neurogenetics.** How genes support the function of neurons

**Neuroleptic malignant syndrome.** Flu-like symptoms such as sweating, fever, and other symptoms such as blood pressure changes and autonomic nervous system irregularities induced by antipsychotic drugs

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

**Neurotoxins.** Substances that damage or destroy parts of the nervous system

**Neurotransmission.** Transmission of information between neurons

**Neurotransmitters.** Signalling chemicals that are synthesized within neurons, are released from neurons, and have effects on neurons or other cells

**Neurotrophins.** A family of molecules that promotes the survival and plasticity of neurons during development and in adulthood

**Nicotine.** Central psychoactive ingredient in tobacco

**Nicotine abstinence syndrome.** Nicotine withdrawal symptoms characterized by craving, irritability, anxiety, hostility, concentration difficulties, impatience, and insomnia

**Nicotine replacement therapy.** Therapy that consists of using a nontobacco nicotine product to minimize symptoms

**Nigrostriatal dopamine pathway.** Set of dopamine neurons with somas in the substantia nigra and axons terminating in the basal ganglia

**Nitrosamines.** Chemicals shown to produce cancerous tumor growth

**Nitrous oxide (or laughing gas).** An inhalant recreationally used for euphoric effects, along with a mixture of depressant and hallucinogenic effects

**Nociception.** Communication of pain sensations in the nervous system

**Nodes of Ranvier.** Uncovered sections of axons between myelin sheaths

**Noncompetitive antagonist.** Drug that does not prevent a neurotransmitter from binding to the receptor but does prevent the neurotransmitter from activating the receptor

**Nonspecific binding.** Binding of a drug to sites that are not the intended target for a drug's effects

**Noradrenergic neurons.** Neurons that synthesize and release norepinephrine

**Nucleus accumbens.** Limbic system structure that facilitates rewarding effects

**Objective effects.** Pharmacological effects that can be directly observed by others

**Obsessive–compulsive disorder (OCD).** Distress arising over obsessions; accompanied by compulsive behavior that endeavors to reduce this distress

**Occipital lobe.** Region of the cerebral cortex important for processing visual information

**Off-label.** A non-government-approved use of a clinically available drug

**Oligodendrocyte.** Glial cell that forms a material called myelin around the axons of neurons

**Open-label studies.** Assignment of study treatments without using blinded procedures

**Opioid overdose.** Overdose from opioid use in the form of severe respiratory depression, accompanied by weakness, weak pulse, bluish color to lips and skin, inability to talk, and, potentially, unconsciousness

**Opioids.** Psychoactive substances that elicit pharmacological effects by acting on opioid receptors

**Opponent-process theory of drug addiction.** The effects of a drug that are automatically counteracted by opposing actions in the body

**Orbitofrontal cortex (role in drug addiction).** A structure within the prefrontal cortex that receives input from the amygdala and may enhance the incentive value of stimuli

associated with drug use; may elicit cravings when the drug is absent

**Out-of-body experience.** The sensation of floating above one's body or even viewing one's body as if one is separate from it

**Oxytocin.** Pituitary hormone important for uterine contraction during childbirth; also contributes to milk letdown during breast-feeding

**Panic attacks.** An abrupt and possibly unexpected strong physiological reaction accompanied by intense apprehension, fearfulness, or terror

**Panic disorder.** Repeat occurrences of panic attacks

**Parasympathetic nervous system.** Subsystem of the autonomic system that is dominant during relaxed states, including decreases in heartbeat, stimulation of digestion, and the closing of airways

**Parker, Quanah.** Comanche chief who advocated using peyote in religious ceremonies

**Parietal lobe.** Region of the cerebral cortex important for processing touch information

**Partial agonist.** Drug that possesses a weaker efficacy for activating receptors than a full agonist

**Partial opioid receptor agonists.** Drugs that produce partial agonist actions at $\mu$ opioid receptors

**Passive diffusion through the blood–brain barrier.** Blood–brain barrier penetration by lipid-soluble, uncharged, small substances

**Percentage alcohol (or alcohol by volume).** Number of grams of alcohol found in 100 milliliters of solution

**Periaqueductal gray.** Small layer of tissue that surrounds the cerebral aqueduct

**Persistent depressive disorder (or dysthymia).** A disorder that includes a depressed mood that occurs nearly every day for at least two years

**Personalized medicine.** Method of prescribing treatments most appropriate for a patient's unique biological makeup

**Pharmacodynamic tolerance.** Reduced responsiveness to a drug at the drug's site of action

**Pharmacodynamic tolerance to alcohol.** Reduced physiological responsiveness to alcohol's pharmacological actions

**Pharmacodynamics.** The physiological and biochemical actions of drugs

**Pharmacogenetics.** The study of how genetic differences influence a drug's pharmacokinetic and pharmacodynamic effects

**Pharmacokinetic tolerance (or drug dispositional tolerance).** Pharmacokinetic actions that reduce the amount of drug reaching its site of action

**Pharmacokinetics.** A drug's passage through the body

**Phase I biotransformation.** First biotransformation phase for a drug that normally involves P450 enzymes and produces a water-soluble metabolite

**Phase II biotransformation.** Second biotransformation phase occurring through conjugation of a drug's metabolites, making them resistant to passive diffusion

**Phencyclidine.** A commonly abused dissociative anesthetic

**Phytocannabinoids.** Cannabinoids derived from cannabis plants

**Placebo.** Substance identical in appearance to a drug but physiologically inert

**Polydrug use.** The use of multiple substances, normally with the intention of achieving a specific effect

**Polymorphism.** A difference in the encoding of a gene compared to the most common sequence in a population

**Pons.** A hindbrain structure that elicits startle reflexes

**Positive modulator.** A chemical substance that binds to an allosteric site on a receptor and increases the ability of a neurotransmitter to bind to and/or activate the receptor

**Positive symptoms.** Addition of abnormal behaviors such as hallucinations, delusions, and thoughts of persecution in schizophrenia

**Post-traumatic stress disorder (PTSD).** Persistent state of physiological arousal or exaggerated response to certain stimuli, particularly those associated with a traumatic event

**Potency.** Amount of drug used to produce a certain level of effect

**Predictive validity.** How well a model predicts treatment effects

**Prefrontal cortex.** Most anterior part of the frontal cortex; an integration area for all types of sensory input; initiates movements

**Probiotic.** Live bacteria taken for beneficial physiological effects

**Prodromal phase of schizophrenia.** Schizophrenia-like symptoms that occur less frequently and with less severity than the symptoms found in schizophrenia

**Prodrug.** A physiologically weak or inactive compound metabolized in the body to produce an active drug

**Proof of alcohol.** Numerical value that is double the percentage of alcohol

**Propagation of action potentials.** Series of action potentials occurring in succession down an axon

**Propeptide.** Chain of amino acids containing one or more peptides

**Protein kinase.** Enzyme that causes phosphorylation of a substrate protein

**Pseudo-hallucinations.** Altered perception of things that are real

**Psilocybin.** Main psychoactive constituent in hallucinogenic mushrooms belonging to the genus *Psilocybe*

**Psychedelic antidepressant drug.** An approved drug for the treatment of depression that can produce a psychedelic experience

**Psychedelic drugs.** Drugs that induce a reality-altering experience consisting of hallucinations, sensory distortions, or delusions

**Psychoactive drugs.** Drugs that affect mood, perception, thinking, or behavior by acting in the nervous system

**Psychopharmacology.** Study of how drugs affect mood, perception, thinking, or behavior

**Psychostimulant-induced psychosis.** Psychotic behavior caused by psychostimulant use

**Psychostimulants.** Drugs that increase psychomotor and sympathetic nervous system activity as well as improve alertness and positive mood

**Psychotropic drug.** Drug used to treat a psychological disorder

**Punding.** Psychostimulant-induced stereotypy in humans

**Pure opioid receptor agonists.** Drugs that act as full receptor agonists at $\mu$ opioid receptors

**Pure opioid receptor antagonists.** Drugs that act as full receptor antagonists at $\mu$ opioid receptors

**Purposeful behavior (for psychostimulant use).** Behavior that is goal directed; increased by lower doses of psychostimulants

**Purposeless behavior (for psychostimulant use).** Non-goal-directed behavior; may appear as habits; increased by higher doses of psychostimulants

**QT interval prolongation.** Prolonged heartbeat as revealed from the QT interval of an electrocardiogram

**Racemic.** A mixture containing equal amounts of both optical isomers of a compound

**Rapid detoxification.** Detoxification process lasting as long as 10 days and using opioid antagonist administration in a treatment facility

**Rate-dependent effects.** Differing effects of a drug depending on the rate of behavior prior to drug administration

**Rate-limiting step.** Slowest conversion rate in a synthesis process

**Rave.** Large organized party held in a dance club or warehouse where electronic dance music is played with a light show

**Receptor.** Protein located in a neuron membrane that can be bound to and activated by a neurotransmitter

**Receptor efficacy.** Drug's ability to alter the activity of a receptor

**Receptor tyrosine kinase.** A family of metabotropic receptors not coupled to a G protein; instead intracellular signalling relies on phosphorylization of a tyrosine kinase molecule located on the intracellular portion of the receptor

**Recreational drug use.** Using a drug entirely to experience the drug's effects

**Refractory period.** Period following an action potential when the neuron resists producing another action potential

**Reinforcement.** Process in which the resulting consequence from a response increases the frequency of future responses

**Relapse.** Return to a chronic drug use state that meets the clinical features of a substance use disorder

**Resting potential.** Negatively charged local potential that a neuron maintains as a stable level

**Reticular activating system.** System of structures that support arousal in the cerebral cortex

**Reuptake.** Return of neurotransmitters to the axon terminal via membrane transporters

**Reversible drug-induced dementia.** Reversible drug-induced dementia characterized by stupor and anterograde amnesia

**Reversible MAO inhibitors.** Antidepressant drugs that either temporarily bind to MAO or allow other compounds to displace the drug from MAO

**RIMA drugs (reversible inhibitors of $MAO_A$).** Antidepressant drugs that selectively inhibit $MAO_A$ but allow for displacement from $MAO_A$ by tyramine

**Safety pharmacology.** The study of a drug's adverse effects

**Salvinorin A.** Psychoactive compound found in *Salvia divinorum*, referred to as *magic mint* or *diviner's sage*

**Schizophrenia.** Severe, lifelong mental illness consisting of disturbed thinking, abnormal behavior, an inability to understand what is real, and an impaired processing of emotions

**Second messenger.** Intracellular signalling molecule produced following the activation of another protein by an extracellular molecule, such as a neurotransmitter

**Secondhand smoke.** Smoke exhaled from a smoker or smoke released from a burning tobacco product

**Sedative-hypnotic.** A drug that produces both calming (sedative) and sleep-inducing (hypnotic) effects

**Selective $MAO_B$ inhibitors.** Antidepressant drugs that primarily inhibit $MAO_B$ enzymes and exhibit weaker inhibition of $MAO_A$ enzymes

**Selective serotonin reuptake inhibitor (SSRI).** Antidepressant drug that elevates serotonin levels by blocking reuptake through serotonin membrane transporters

**Semisynthetic opioids.** Opioid drugs synthesized from morphine or codeine

**Sensitization.** An adaptation that increases a drug's effects

**Sensitization to alcohol.** Increase in alcohol's efficacy, especially its reinforcing effects

**Sensory neuron.** Neuron that conveys sensory information via axons to the central nervous system

**Sensory-gating deficit.** A schizophrenic's diminished capacity to filter out unimportant stimuli in his or her environment

**Serotonin discontinuation syndrome.** Syndrome caused by abrupt withdrawal of an antidepressant drug, resulting in sensory disturbances, sleeping disturbances, disequilibrium, flu-like symptoms, and gastrointestinal effects

**Serotonin syndrome.** Antidepressant-drug-induced life-threatening condition characterized by agitation, restlessness, disturbances in cognitive functioning, and possibly hallucinations

**Serotonin-dopamine (or $5\text{-}HT_{2A}$-$D_2$ receptor) hypothesis.** Hypothesis stating that atypical antipsychotic drug effects derive from preferential antagonism of serotonin $5\text{-}HT_{2A}$ receptors compared to dopamine $D_2$ receptors

**Serotonin–norepinephrine reuptake inhibitors (SNRIs) (or dual serotonin and norepinephrine reuptake inhibitors).** Antidepressant drugs that enhance levels of serotonin and norepinephrine by blocking serotonin and norepinephrine membrane transporters

**Set and setting.** Influence of mindset and physical surroundings on a psychedelic experience

**Sexual side effects.** Sexual dysfunction, including erectile dysfunction, inability to achieve orgasm, and loss of sexual drive caused by antidepressant drugs

**Short-term opioid detoxification.** Detoxification process that lasts as long as 30 days and usually uses opioid receptor agonists

**Single-blind procedure.** When researchers do not inform study participants which treatment or placebo they received

**Sleep-related complex behaviors.** Complex behaviors that occur while sleeping, including walking, driving, cooking, eating, and carrying on conversations

**Smokeless tobacco.** A tobacco form intended for absorption in the mouth

**Social anxiety disorder.** Fear of being in or performing in social or public situations

**Sodium–potassium pump.** Neuronal membrane mechanism that brings two $K^+$ ions into the neuron while removing three $Na^+$ ions from the neuron.

**Somatic nervous system.** System responsible for delivering voluntary motor signals from the central nervous system to muscles throughout the body and for conveying sensory information from the body to the central nervous system

**Specific phobias.** Significant anxiety provoked by exposure to specific feared objects or situations

**Standard drink.** Drink that contains 14 grams of 100 percent alcohol; equivalent to about 2/3 fluid ounces

**Steady state (for drug concentrations).** A sustained concentration level of drug in the body

**Stereotypy.** Psychostimulant-produced purposeless behavior

**Street name.** An alternative name applied to a recreational or abused substance

**Subjective effects.** Pharmacological effects that cannot be directly observed by others

**Substrate protein.** Protein, following activation of a protein kinase, that may consist of an ion channel, enzyme,

neurotransmitter receptor, or other proteins involved in neuronal processes

**Sudden sniffing death syndrome.** Death occurring from inhalant overdose

**Sympathetic nervous system.** Subsystem of the autonomic nervous system that prepares the body for rigorous activity by increasing heartbeat, inhibiting digestion, and opening airways, among many other involuntary functions

**Synapse.** Components that make up a connection between neurons that includes an axon terminal, postsynaptic terminal, and synaptic cleft

**Synaptic vesicle (or neurotransmitter vesicle).** A vesicle that stores and protects neurotransmitters

**Synergistic drug effects.** The magnitude of the combined drug effect is beyond the sum of each drug's effect alone

**Synesthesia.** Experiencing sensory stimuli in an incorrect sensory modality

**Synthetic cannabinoids (or synthetic marijuana).** Drugs that act on cannabinoid receptors, but do not consist of components from cannabis plants

**Synthetic opioids (or fully synthetic opioids).** Opioids not derived from morphine, codeine, or any other naturally occurring opioid

**Tar.** Particles released from burning tobacco

**Tardive dyskinesia.** Motor disorder primarily affecting muscles of the face that may occur after long-term antipsychotic drug use

**Temporal lobe.** Region of the cerebral cortex important for processing auditory information and supporting language comprehension and production

**Tension reduction hypothesis.** Drinking alcohol reduces stress

**Teratogen.** Substance harmful to a fetus

**Thalamus.** Forebrain structure that routes sensory information from the body to the appropriate lobes

**Therapeutic index.** Ratio of a drug's toxic dose-effect curve value relative to therapeutic dose-effect curve value

**Third-generation antipsychotic drugs.** Drugs that produce antipsychotic effects through a mechanism(s) of action different from those of typical and atypical antipsychotic drugs

**Thirdhand smoke.** Remnants from tobacco smoking gathered on material in the smoker's local environment after smoking has finished

**The 3 Rs.** A review process for animal research that considers "replacement," "reduction," and "refinement" to determine the necessity of using animals, minimum number of animals needed, and procedures to minimize pain and distress

**Tolerance.** An adaptation that weakens a drug's effects, requiring greater doses to achieve desired drug effects

**Transcription factor.** Substance that increases or decreases gene transcription

**Treatment arms.** Number of treatments and doses provided to patients described in a clinical study

**Treatment-resistant depression.** Diagnosis made after successive failed attempts to significantly reduce depressive symptoms

**Treatment-resistant schizophrenia.** Patients with schizophrenia who exhibit minimal or no improvements after two trials with either typical or atypical antipsychotic drugs

**Tricyclic antidepressant drugs.** Antidepressant drugs that inhibit the reuptake of norepinephrine and serotonin and function as antagonists for various receptors

**Trip.** Hallucinogenic experience

**True hallucination.** Perception of images or sounds that are not real

**Tubero-infundibular dopamine pathway.** Set of dopamine neurons with somas in the hypothalamus and axons terminating in the pituitary gland, where it plays an important role in the secretion of prolactin

**Turnover of neurotransmitters.** The conversion of a neurotransmitter to a metabolite

**Twelve-step anonymous programs.** A type of substance addiction program where anonymous members give testimonies in group settings and follow an outline of 12 steps toward recovery

**Type I alcohol addiction.** Alcohol addiction that occurs at age 25 or older, has low genetic risk, and exhibits high psychosocial risk

**Type I bipolar disorder.** Type of bipolar disorder that exhibits depression and episodes of severe mania

**Type II alcohol addiction.** Alcohol addiction that occurs before age 25, exhibits high genetic risk, and has traits associated with poor impulse control

**Type II bipolar disorder.** Type of bipolar disorder that exhibits depression along with episodes of less-severe mania

**Typical antipsychotic drugs (or first-generation or classical antipsychotic drugs).** Class of antipsychotic drugs that reduce the positive symptoms of schizophrenia, have weak efficacy for negative symptoms and cognitive impairment, and produce extrapyramidal side effects at therapeutic doses

**Ultra-rapid opioid detoxification.** Detoxification process lasting as long as two days and using opioid antagonist administration in a hospital setting

**Upregulation.** Increased production of proteins

**Vaping.** Inhaling vapor from an e-cigarette

**Vascular depression.** Depressed symptoms associated with poor blood flow in the brain

**Vasopressin.** Antidiuretic hormone that causes the kidneys to absorb water from the bloodstream

**Ventricles.** Cerebrospinal fluid-filled cavities in the brain

**Vesicular transporter.** Channel located on a vesicle that allows passage of neurotransmitters

**Vigilance.** A state of readiness for detecting and responding to unpredictable events

**Voltage-gated ion channels.** Channels that open or close, depending on local potential changes

**Wernicke-Korsakoff syndrome.** Condition caused by heavy, long-term alcohol use resulting in memory loss, false memories, poor insight, apathy, and tremors

**Wine.** An alcoholic beverage, usually with 12–15 percent alcohol content, made through fermentation of fruit

**Withdrawal syndrome.** The collection of withdrawal symptoms for a drug

**Z-drugs (or non-benzodiazepine hypnotics).** Sleep aids whose generic names usually start with a *Z* and that act by binding to BZ I sites

**Zero-order kinetics.** The elimination of a drug in non-half-lives

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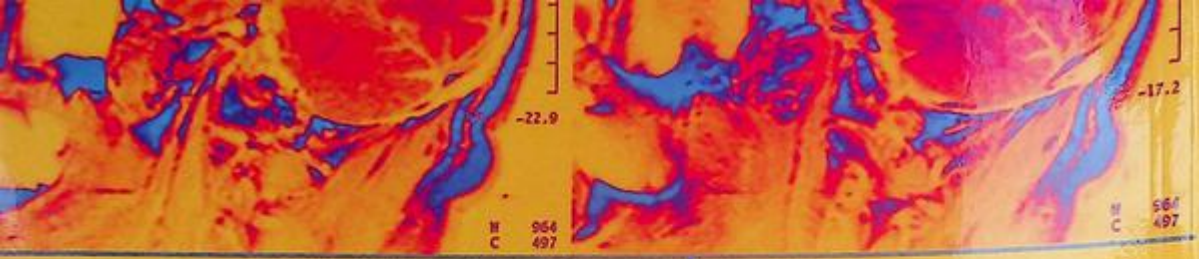

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Printed in Canada

Cover image: iStock.com/dem10

ISBN 978-1-5443-6257-1

SAGE www.sagepublishing.com
Los Angeles | London | New Delhi | Singapore | Washington DC | Melbourne