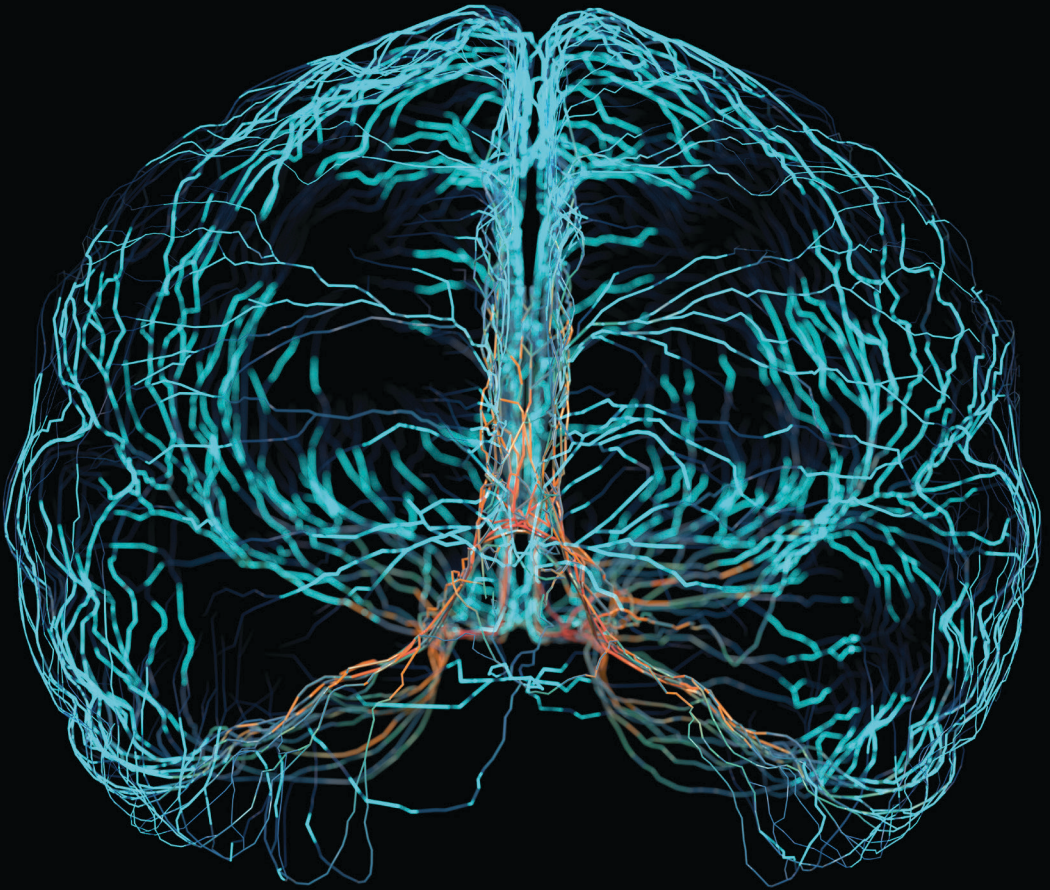


JOHN BRICK

DRUGS, THE BRAIN, AND BEHAVIOR

THE PHARMACOLOGY OF THERAPEUTICS AND DRUG USE DISORDERS

THIRD EDITION



“Drugs, the Brain and Behavior is a must have for those in any related field of medicine or academics. Either as a reference, or to simply enjoy from cover to cover, it will provide the reader with an in depth, but easy to understand comprehensive review of how drugs influence the brain to produce the different behaviors, both good and bad, that we observe clinically.”

Lee Tessler, MD, FACS, FAANS, Chief of Neurosurgery,
NYU Langone Hospital – Long Island, NY, USA

“The latest edition of Drugs, the Brain and Behavior provides excellent, up-to-date information on drug actions on the brain and their impact on society and individual behavior. The medical consequences of therapeutics and drug use disorders and treatment updates are particularly useful. Moreover, complex topics in pharmacology and neurochemistry are explained clearly and provide a valuable resource of information for a wide audience including health care professionals.”

Larissa A. Pohorecky, PhD, Professor of Pharmacology (Emeritus),
Rutgers University Center of Alcohol and Drug Studies,
Piscataway, NJ, USA

“As a clinician and researcher in maternal child health for over thirty years, “Drugs, the Brain and Behavior: The Pharmacology of Therapeutics and Drug Use Disorders” is my go source to incorporate this continually evolving area into my practice.

Dr Brick includes specifics on various drugs relating to recreational and clinical situations, and how they affect the human brain. He relays his years of research into a concise resource that is a benefit for the clinician.

“Drugs, the Brain and Behavior: The Pharmacology of Therapeutics and Drug Use Disorders” Edition III is a leading source of information that is a true must have !!!!”

William P Stanell, MD FACOG, Fellow American College of
Obstetrics and Gynecology, USA



Taylor & Francis

Taylor & Francis Group

<http://taylorandfrancis.com>

Drugs, the Brain, and Behavior

This third edition of *Drugs, the Brain, and Behavior* provides a comprehensive overview of the brain and explores the clinical and pharmacological issues surrounding drug abuse and dependence.

Dr Brick provides definitions, historic discoveries about the nervous system, and original, eye-catching illustrations to discuss the brain/behavior relationship, basic neuroanatomy, neurophysiology, and the mechanistic actions of mood-altering drugs. Topics include: how psychoactive drugs affect cognition, behavior, and emotion; the brain/behavior relationship; the specific effects of major addictive and psychoactive drug groups; new definitions and thinking about abuse and dependence; and the medical uses of drugs, such as cannabinoids. A new chapter on biobehavioral markers explores how markers can guide the clinician in the diagnosis of some disorders is included. This book offers a quick reference guide which uses a balance of instruction, illustrations, tables, and formulas, that will give you a broad, lasting introduction to this intriguing subject.

Drugs, the Brain, and Behavior is an invaluable resource for students in the field, nurses, psychologists, counsellors, physicians and other health care professionals.

John Brick, Ph.D., M.A., F.A.P.A. is a highly published author in psychopharmacology and the biomedical effects of alcohol and other drugs, national and international lecturer, and neuroscience trained research scientist in biological psychology.



Taylor & Francis

Taylor & Francis Group

<http://taylorandfrancis.com>

Drugs, the Brain, and Behavior

The Pharmacology of Therapeutics
and Drug Use Disorders

3rd Edition

JOHN BRICK

Designed cover image: MediaProduction © Getty Images

Third edition published 2024

by Routledge

605 Third Avenue, New York, NY 10158

and by Routledge

4 Park Square, Milton Park, Abingdon, Oxon, OX14 4RN

Routledge is an imprint of the Taylor & Francis Group, an informa business

© 2024 John Brick

The right of John Brick to be identified as author of this work has been asserted in accordance with sections 77 and 78 of the Copyright, Designs and Patents Act 1988.

All rights reserved. No part of this book may be reprinted or reproduced or utilised in any form or by any electronic, mechanical, or other means, now known or hereafter invented, including photocopying and recording, or in any information storage or retrieval system, without permission in writing from the publishers.

Trademark notice: Product or corporate names may be trademarks or registered trademarks and are used only for identification and explanation without intent to infringe.

[First edition published by Haworth Medical Press]

[Second edition published by Routledge 2013]

ISBN: 978-1-032-42040-0 (hbk)

ISBN: 978-1-032-41978-7 (pbk)

ISBN: 978-1-003-36094-0 (ebk)

DOI: 10.4324/9781003360940

Typeset in Dante and Avenir

by Newgen Publishing UK

Contents

<i>About the Author</i>	ix
<i>List of Figures and Tables</i>	xi
<i>Preface</i>	xv
<i>Acknowledgements</i>	xvii
<i>Introduction</i>	xviii
1 What Is a Drug?	1
2 The Brain–Behavior Relationship	11
3 Pharmacokinetics	20
4 Functional Neuroanatomy: Where Do Psychoactive Drugs Act?	40
5 Neurophysiology: How Do Psychoactive Drugs Act?	53
6 Antidepressants: Drugs That Lift Us Up	66
7 Anxiolytics: Drugs That Calm Us Down at a Cost	82

8 Antipsychotics: Drugs That Make Us Sane	97
9 Stimulants: Drugs That Make Us High	114
10 Alcohol: The Socially Accepted Addictive Drug	133
11 Opioids: Drugs That Calm Our Pain	170
12 Inhalants: A Matter of Life and Breath!	191
13 Marijuana: The Sometimes Illegal Recreational Plant	197
14 Hallucinogens: Altering Reality or Helping?	225
15 Nicotine: Of What Value?	238
16 Addiction: The Chronic Medical Illness	247
17 Biobehavioral Markers of Substance Use Disorders	262
18 Forensic Issues in Psychopharmacology	280
<i>Index</i>	298

About the Author

John Brick, Ph.D., M.A., F.A.P.A. is a research scientist and educator with more than 45 years of experience in alcohol and drug studies. He is Executive Director of Intoxikon International and in private practice in forensic psychopharmacology. During his 27 years at Rutgers University, he was a member of the Graduate Faculty, held positions as Chief of Research at the Center of Alcohol Studies Education and Training Division, Laboratory Director of the Alcohol Behavior Research Lab, Chairman of the Graduate Curriculum on the Biology of Alcohol, Associate Director of the Advanced School of Alcohol and Drug Studies and Forensic Psychopharmacology Consultant to the University. Dr. Brick taught courses in neuropharmacology for 20 years at Rutgers and elsewhere, including DuPont Pharma and Beijing Medical University as part of the World Health Organization's first medical education initiative in Asia. He co-organized and chaired the First International Symposium on Alcohol and Stress and the International Conference on Alcohol and Aggression. Dr. Brick was one of only six Americans invited to address the Russian Academy of Medicine on the occasion of their Centenary Anniversary – the only American working in the field of alcohol and drug studies to receive the distinct honor of presenting his work and representing his country. Dr. Brick is the recipient of the Addiction Service Award for Excellence in Alcohol and Drug Education and the first New Jersey Award for Community Service (MADD). He is also a double Fellow of the American Psychological Association; first for his “outstanding and unusual contributions to the science and profession of psychology” and second in recognition of the “national impact” of his working

in the field of psychopharmacology. He published his first peer reviewed scientific article before starting graduate school and is the author or co-author of more than 100 scientific publications including *Socioeconomic Evaluation of Addiction Treatment* (The White House), the first and second editions of the *Handbook of the Medical Consequences of Alcohol and Drug Abuse* (Haworth Press), *Forensic Alcohol Test Evidence* (C.C. Thomas), and *Drugs, The Brain and Behavior* (Routledge Press), now in its third edition. He completed his undergraduate studies in physiological psychology at Queens College, City University of New York, while he simultaneously received training and conducted neuropharmacology and neurochemistry research at The Rockefeller University (NYC). He completed his graduate work at Binghamton University, The State University of New York. A graduate of a joint degree doctoral program in psychobiology, his training in neuroscience and psychology further focused his research on the relationship between drugs, the brain and behavior and gave him the opportunity to work as a scientific reviewer in both clinical and biological sciences for various federal agencies and leading journals in the field. In 1994 he founded Intoxikon International, a company that provides multi-disciplinary consulting and training in alcohol and drug studies to government agencies, health care professionals, law enforcement, educational institutions and corporations. Dr. Brick lectures throughout the United States and lives and works in Bucks County, Pennsylvania where he designs gardens, composes and is an amateur astronomer.

Figures and Tables

Figures

1.1	BBB model of drug action	8
2.1	Phineas Gage	15
2.2	Intracranial self-stimulation of reward pathways in the brain	17
3.1	Gastrointestinal system. Most psychoactive drugs that are administered orally and that are water soluble and membrane permeable enter the circulation through the upper intestine	23
3.2	From the gastrointestinal system, drugs enter the circulation travelling first to the liver, then continue in the circulation to the rest of the body in a continuous loop	24
3.3	The pulmonary system. Capillaries surround the alveoli and exchange oxygen (O_2) for carbon dioxide (CO_2) as gas tensions change. As the lungs expand and fill the alveoli, high levels of CO_2 in the arterial blood pass through the thin membranes of the alveoli. At the same time, O_2 passes out of the alveoli into the venous circulation of the lung	25
3.4	Cross-sectional view of cells surrounding a capillary in the brain to form the blood–brain barrier	30
3.5	The amount of time required to reduce the initial peak by one-half defines the distribution half-life	32

xii List of Figures and Tables

3.6	Drug potency	34
4.1	Organization of the nervous system	41
4.2	Basic classification of neuron based on structure	43
4.3	Anatomical terms for spatial orientation	44
4.4	Functional anatomy of the cortex	45
4.5	Sagittal (mid-slice) view of the brain, illustrating subcortical structures	46
4.6	Pathways and structures of the brain	47
4.7	Functional anatomy of subcortical limbic system structures	49
5.1	Spatial relationship between two neurons	54
5.2	Dissociation of sodium chloride into two ionic species	56
5.3	Distribution of sodium and potassium ions inside and outside a neuron	57
5.4	Diagram of ion-gated neurotransmission when the receptor gate is open	58
6.1	Structure of monoamines	69
6.2	The mechanism of neurotransmission and serotonin reuptake inhibition is illustrated in Figure 6.2	74
7.1	Benzodiazepine-GABA modulin receptor complex	89
8.1	The effects of chlorpromazine on dopamine	99
8.2	Multifactor model of schizophrenia	102
9.1	Biochemical structures of various sympathomimetics. Insert illustrates biosynthesis of catecholamines	117
9.2	Neuropharmacological action of caffeine	123
10.1	Structure of common alcohols	134
10.2	Different rates of drinking the same quantity of alcohol alter the maximum blood alcohol concentration	139
10.3	Oxidative metabolism of ethanol	143
10.4	Alcohol impairs many domains of cognitive functioning	152
10.5	Craniofacial characteristics of FAS	163
11.1	Harvesting of raw opium from the poppy plant (<i>Papaver somniferum</i>)	173
11.2	Chemical structures of various opioids and the opioid antagonist naloxone	174
13.1	Cannabis plant	198
13.2	The cannabis plant is used in the manufacture of many legal products. Compounds such as delta-9-tetrahydrocannabinol (shown) or cannabidiol are primarily responsible for the psychoactive effects of marijuana and hashish, respectively (Adapted from Phillips, 1985)	201

16.1	Mesolimbic dopamine system (MDS)	252
18.1	Flow chart of the scientific parameters in calculating the BAC over time	290

Tables

3.1	Relation of Half Life to Drug Concentration	33
3.2	Pharmacological Bases of Drug Interactions	36
4.1	Spatial Neuroanatomical Terms	44
4.2	Biobehavioral Functions of the Hypothalamus	49
4.3	Functional Aspects of the Cranial Nerves	51
5.1	Neurotransmitters and Identified Functions	59
5.2	Dietary Precursors of Common Neurotransmitters	61
6.1	Types and Features of Mood Disorders	67
6.2	Pharmacological Treatment Categories for Clinical Depression	68
6.3	Frequently Prescribed Antidepressants	76
6.4	Reported Side Effects of Antidepressants in Some Patients	78
6.5	Signs and Symptoms of Antidepressant Withdrawal	79
7.1	Biobehavioral Symptoms of Anxiety	84
7.2	Dose Guidelines for Sedation	93
7.3	Benzodiazepine Withdrawal Symptoms	94
8.1	Major Categories and Pharmacology of Antipsychotics	103
8.2	Major Dopamine Pathways	107
8.3	Anticholinergic Side Effects	110
9.1	Associated Biobehavioral Effects of Stimulants	123
10.1	Biobehavioral Effects of Alcohol Intoxication	149
10.2	Major Categories and Common Signs of Alcohol Intoxication	150
10.3	Relative Injury Risk: Effect of Mode, Age, Gender and BAC	155
10.4	Stages of Alcoholic Liver Disease	162
11.1	Pharmacological Characteristics of Common Opioids	176
11.2	Signs and Symptoms of Opioid Intoxication	181
11.3	Signs and Symptoms of Opioid Withdrawal	185
12.1	Commonly Used Inhalants	192
12.2	Biobehavioral Effects of Inhalants	194
12.3	Signs and Symptoms of Inhalant Withdrawal	194
12.4	Major Medical Consequences of Inhalant Use	195
13.1	Common Subjective Effects of Marijuana Intoxication	208
13.2	Signs and Symptoms of Marijuana Withdrawal	218

xiv List of Figures and Tables

14.1	Common Hallucinogens Available Around the World	228
14.2	Signs and Symptoms of Hallucinogen Use	234
15.1	Signs and Symptoms of Nicotine Withdrawal	243
16.1	DSM-5 Criteria for Substance Use Disorder	250
16.2	DSM-5 Symptoms of Withdrawal	251
16.3	Common Medications to Treat Chemical Dependencies	256
17.1	Biobehavioral Markers for Acute Intoxication	264
17.2	Detection Windows for Common Drugs of Abuse	266

Preface

The best investment you can make in life is in your education. The second-best investment is in the education of others. That is, in part, the motivation to write *Drugs, The Brain and Behavior*. To learn how something interesting works and then teach others is a rewarding experience for all involved.

My undergraduate training in physiological psychology and early career training in neuropharmacology at The Rockefeller University narrowed my focus on the physiological basis of behavior and in particular, how psychoactive drugs like alcohol changed the brain. As a research scientist I was unencumbered with teaching responsibilities, but during our weekly lab meetings, the excitement and hunger for more information was palpable. I eventually found myself teaching and enjoyed sharing my knowledge through courses such as *Drugs and the Brain*, *Neuropharmacology* and *Clinical Psychopharmacology*. I once asked John L. Fuller, the distinguished scientist who founded the field of Behavior Genetics, if after his long career, he satisfied his goals. He told me that his goal was to produce students smarter than himself. Another scientist, Nobel Laureate, H. Keifer Hartline, told me that anything of scientific greatness would be difficult to summarize in a few words, but that's what made science so interesting. The knowledge-sharing challenge inspired by these luminaries often comes to mind in my writings, lectures and when my students ask interesting and complicated questions.

Drugs, The Brain and Behavior developed as a result of requests from graduate and post-graduate professionals enrolled at Rutgers University where I taught for many years and from diverse audiences attending my various lectures

throughout the country. There has been no shortage of questions on this topic and without questions, there are no answers. In the third edition of DBB-3, we continue to provide a solid foundational understanding of how the brain works and the behavioral, medical and physiological effects of psychoactive drugs including therapeutic medications often used to treat patients with co-morbid disorders. I hope that readers continue to enjoy learning about developments in the field from the third edition of *Drugs, The Brain and Behavior: The Pharmacology of Therapeutics and Drug Use Disorders*, and continue to ask questions about our amazing brain.

John Brick, Ph.D., M.A., F.A.P.A.

Acknowledgements

I am happy to thank the following people for their help in DBB-3. Thanks to Lisa Rickert for her incredible patience and organizational skills. She keeps everything in this busy office (including me) on schedule. Thank you, Lisa. Thanks also to Karen Gutwirth who illustrated most of the figures in this and other publications, Dr. Carlton Erickson, and to my publisher for their continued interest, support and patience.

Most of all, thanks to Laurie Stockton who for nearly fifty years has steadfastly supported my interests. Who else would take midnight drives to the lab so I could get an early start analyzing data from the scintillation counter, provide a fresh perspective on everything and always encourage me to pursue my passions? You are the best and for all of these things, this book is dedicated to you.

Introduction

How to Get the Most from *Drugs, the Brain and Behavior*

The greatly expanded and updated third edition of this book is designed to provide a sound foundation of how the brain works and how drugs affect the brain to change behavior. Readers will get the most from *Drugs, the Brain and Behavior* by reading it in the order it is written. It is a story that develops and builds on previous chapters. Beginning with the definition of a drug and terminology used throughout the book, the story starts with the brain, beginning with the historical step-by-step discoveries that led to the relationship between the brain and behavior. On the heels of those discoveries was a window on how brain cells function and the startling discovery that mental illness is neurochemical in nature. A review of the neuropharmacology of therapeutic medications makes the brain-behavior relationship more understandable, particularly because many drug use disorders have co-morbid psychiatric illnesses requiring pharmacotherapy. Finally, *Drugs, the Brain and Behavior* explains the essential neuropharmacology of psychoactive drugs used to get high. With a working knowledge of drug actions, the reader will find the drug chapters useful as go-to references about the pharmacokinetics, pharmacodynamics, medical consequences and forensic implications of therapeutic and illicit drugs.

What Is a Drug?

1

We begin *Drugs, the Brain, and Behavior* with the realization that traditionally, drugs are therapeutic chemicals designed to have maximal benefit with minimal risk of side effects or toxicity. In this book, we describe psychoactive drugs—those drugs that change the way we think, feel and behave by changing the functioning of the brain. The recurrent theme in DBB is that all psychoactive drugs exert their effects by altering brain neurochemistry. In other words, all drugs that make us feel up (e.g., stimulants), down (depressants), normal (therapeutic drugs, mostly) or “sideways” (adverse consequences of acute or chronic use) only do so by changing the brain. Our journey begins with defining drugs, the development of modern therapeutic medications and the introduction of a model of drug action to understand how drugs work.

Thousands of drugs are currently available, with new drugs constantly under development every day. Drugs come in many forms. Alcohol is a drug, as are, for example, heroin, caffeine and Prozac. Each one produces unique changes in feelings and behavior. These drugs are by definition “psychoactive drugs” because they produce their behavioral effects by changing the brain. Antibiotics are also drugs, but they are not considered psychoactive, even though your behavior may change (i.e., you may feel better after they have fought off a debilitating infection). Psychopharmacology is the study of the use, mechanisms, and effects of drugs that act on the brain and subsequently alter behavior. Therefore, the definition of a drug varies with its biological and behavioral (biobehavioral) action. In *Drugs, the Brain, and Behavior*, we will primarily be discussing psychoactive drugs.

2 What Is a Drug?

Drug use is not new, despite the fact that every generation thinks that its drug problem is somehow unique. On the contrary, drug use is as old as recorded history, although effective psychotherapeutic drug use is a relatively recent development. For example, alcohol in the form of mead was popular in the Paleolithic age (8000 B.C.), the use of opium is reported in Sumerian tablets (4000 B.C.) and marijuana was known in China in 2737 B.C.

Psychotherapeutic drugs (those used to restore mental health) are, by comparison, very new. If the last 8,000 years of drug use were placed on a 24-hour timeline, and started at 00:01 a.m., the Golden Age of therapeutic drug development and the dawn of a scientific understanding of how drugs work, began somewhere around 11:45 p.m.! In other words, although humans have been altering their mental and physical state with drugs for many thousands of years, our understanding of psychopharmacology is very recent.

Illicit drugs used to get “high” are too common to list and ever changing. Often street names reflect their effect of appearance (e.g., uppers, downers, reds, weed, ecstasy). Psychotherapeutic medications also have different names: chemical, molecular, generic, and trade or brand name. For example, illustrated below are different ways of describing the commonly prescribed antianxiety drug, Xanax. (Note that according to Medical Transcriptionists (MT) Desk Reference and Style Guide, brand names are proper nouns and always capitalized; generic drug names are common nouns and not capitalized. We will use this style throughout this book.

Trade or Brand Name:	Xanax
Generic Name:	alprazolam
Molecular Formula:	$C_{17}H_{13}ClN_4$
Chemical Name:	8-Chloro-1-methyl-6-phenyl-4Hs-triazolo [4, -δ] [1,4] benzodiazepine

Terminology Used throughout This Book

The terminology of drinking and drugging is difficult, since there is no agreement among institutions or authors about the proper words to use. Later in this book we discuss the Diagnostic and Statistical Manual for Mental Disorders or DSM-V (Chapter 16) medical classifications of “substance, chemical, or drug abuse”, “substance, chemical, or drug dependence”, and

“substance use disorders”. The terms “binge drinking”, “social use”, “moderate use”, “heavy drinking”, “problem drinking”, and “unhealthy use” of alcohol are relatively common throughout popular and scientific use but unless operationally defined potentially problematic and misused. For the purposes of this book (and reader understanding) we will use drug “abuse”, drug “misuse”, drug “overuse”, “addiction”, and “dependence”.

To begin, we have to agree that the term “drug use” is very broad, but in this book we will use it to mean only the legal, expected, normal, prescribed, or social use of a drug, in cases where no harm is expected from the usual use of the drug.

But now, things get more difficult. It is clear that the terms “abuse” and “dependence” do not appear in the current edition of the Diagnostic and Statistical Manual (DSM-V). Many professionals, exemplified by authors such as White and Kelly argue that the term “abuse” is outmoded, stigmatizing, and technically incorrect. The same is not true for the word “dependence,” which is much more controversial. We believe that both words will continue to be used in common language, and even in our field, so we will continue to use these words throughout this book. Even the scientifically imprecise word “addiction” will be used because it is descriptive and many scientists still use the word freely (see Chapter 16). We will use the word “drug abuse” only in cases where no better term can be found. The word “misuse” (often incorrectly used synonymously in place of “abuse”) technically applies to the incorrect use of prescription drugs; for example, when a patient uses a larger dose than prescribed, or when a left-over antibiotic is used months after the first infection has disappeared, or when a child is given an adult’s prescription for a powerful antihistamine. We will use the word “misuse” in such situations throughout this book.

Another phrase, “drug overuse”, is a form of drug “misuse” in which drugs are taken in higher doses (or for a longer time period) than prescribed, recommended, or intended. Thus “binge drinking” is alcohol “overuse”, and “binge using” of any drug (e.g., cocaine, methamphetamine, or heroin) is drug “over-use”. Again, the term “drug overuse” will be used in these limited situations. But what is it called when Adderall (amphetamine), prescribed by a physician for an adolescent’s ADHD, is used by his college roommate to study? (Is it “use”, “misuse”, or “abuse”, and does it matter what it is called?) In this book, we will call such situations, and others like it, a “drug use problem”, and those who do this, we will call “problem drug users”. Precision in terminology leads to better understanding!

4 What Is a Drug?

Here are some definitions used throughout this book:

- **Drug use** – the legal, expected, normal, prescribed, or social use of a drug, in cases where no harm is expected from the prescribed or recommended use of the drug.
- **Drug abuse** – a general term, analogous to the older DSM-IV definition of “substance abuse”, in which drug use is voluntary, but use causes adverse effects to the individual and to those around the drug abuser.
- **Drug misuse** – the incorrect use of (mainly) prescription drugs.
- **Drug overuse** – a form of drug misuse (mainly prescription drugs) in which drugs are taken in higher doses (or for a longer time period) than prescribed or recommended.
- **Drug dependence** – a brain disease in which impaired control over drug use is the main symptom, in which people cannot stop using without help of some kind, either through formal treatment or 12-step programs (note: drug dependence is *not* the same as physical dependence, which is characterized by withdrawal signs and symptoms upon cessation of drug use).
- **Addiction** – a broad term, less scientific than drug dependence, describing the inability of a person to stop using a drug or a behavior even under adverse conditions; usually used interchangeably with drug dependence by scientists, but used more broadly (often inaccurately) by the general population and the media to describe any drug use or behavior that is perceived to be out of control, or compulsive.
- **Drug Use Disorder** – a mental disorder affecting the brain and behavior leading to the inability to control the use of substances, including legal and illegal drugs (e.g., alcohol, medications). As you can see, there is overlap among these definitions now and probably will be as we continue to understand and define these concepts.

To put this all together, and as an example you might find in this book, a person who uses marijuana once a month would be called a “marijuana user”. (Note: this terminology does not relate to whether a drug is used legally or not). A person who uses marijuana recreationally, 3–4 times a week, and who has chronic bronchitis due to pot smoking, would be called (in this book), a “problem marijuana user”. Finally, a person who uses marijuana every day, has tried to stop, but cannot, and who requires treatment, would be said to have a “severe marijuana use disorder”, based upon the DSM-V criteria.

The Dilemma of Prescription Drug Misuse, Overuse and Addiction

Prescription drug misuse, overuse, and addiction (drug dependence) continues to be a major problem in the United States. One could speculate that the problem is caused by the rising cost of illegal drugs, and/or a greater availability of prescription medications (foreign online ordering, overprescribing by physicians, medication theft from pharmacies or relatives, sharing medications, doctor shopping, black market sales, etc.), or that people have a greater need to abuse drugs to overcome the pain of poverty, joblessness, divorce or the current unfettered flow of drugs across our borders but all of the factors relate to two concepts: supply and demand. Unfortunately, we don't know the major reasons.

The three drug classes that contribute most to the prescription medication dilemma are benzodiazepines (anxiolytics), opioids and amphetamines. Illegal use of drugs has increased, particularly the use of highly potent opioids, such as fentanyl. Many clues to solving the dilemma can be found in the later chapters on anxiolytics, opioids, and cocaine and other stimulants.

Golden Age of Pharmacology

A major breakthrough in our understanding of how proactive drugs work came about by accident during the 1950s, known as the Golden Age of Pharmacology. New drugs promised great hope in providing treatment of mental illness and restoring mental health. Many of these promises have been kept. For example, some forms of schizophrenia, previously untreatable, are often effectively treated with antipsychotic medications that enable the patient to engage in a meaningful psychotherapeutic relationship and to function in society. While antipsychotics have replaced lobotomies (a dreadful digression in the treatment of the mentally ill), psychosurgery is still used in epileptics and Parkinson's patients as a treatment of last resort. Nevertheless, the advent of antidepressants (Chapter 6) and antianxiety drugs (Chapter 7) has enabled many patients to resume normal lives in a complex society.

Treatment of mental illness with drugs is not a panacea, and some advances have not been without problems. For example, these medications do not work for all patients. There are also side effects, such as motor function disorders (e.g., tardive dyskinesia) in the case of some antipsychotic medications.

6 What Is a Drug?

Another side effect is a “serotonin syndrome” that may follow high doses of some antidepressants or other drugs or dietary supplements that increase brain serotonin. Long term use of anxiolytics has also been associated with dependency and other psychiatric problems (see Chapter 7). Also, not all patients in need are successfully treated with psychotherapeutics. The unintended consequences of a drug (i.e., adverse side effects) must always be weighed against the therapeutic effectiveness of the drug. This is called “risk-to-benefit decision making,” which is at the heart of the prescribing physician, nurse practitioner or (in some states) a prescribing psychologist.

The use of psychotherapeutic medications in the United States is widespread. About one in six women and one in fourteen men use psychoactive prescription drugs. About 100 million prescriptions for antianxiety drugs are written in the United States each year. Similarly, illicit psychoactive drug use is quite common and is discussed in relevant chapters of this book.

Why Study a Brain – Behavior Relationship in the Next Chapter?

Ultimately, it is the brain that responds to, processes, and initiates all behavior, whether normal or pathological. We learned earlier that psychoactive drugs alter behavior. Prior to discussing the nuts and bolts of neurophysiology and neuropharmacology, let’s carefully examine the basic elements of behavior that you may be familiar with. As behaving organisms, we respond to various events in our environment in many different ways. These events can act as stimuli to trigger certain responses or associations. Consider what you are doing right now, reading. For the moment, think of how the words on this page and the meanings that they represent act as stimuli. In their most basic form, the letters and groups of letters (words) are nothing more than two-dimensional curvilinear visual stimuli that fall on very specialized cells in the back of your eyes. These cells are called visual receptors, one of many different types of receptors in the body. The human eye has two basic types of receptors, one type for color vision and another for monochromatic vision. The images on this page activate entire fields of connected receptors in each eye. Electro chemical information from these receptors is then transmitted from the back of the eye to the optic nerve, which carries the visual information to various parts of the brain, where it is further processed.

In the brain, associations are made between this new incoming information and previously stored information, and resulting in a cognitive association

and response. Shapes become letters, letters become words, words become sentences and, if everything is working properly, some associative meaning occurs and information is transferred from one medium to another (from shapes to meaning) and with amazing symphony of biological activity in between!

Your response to what you read can vary considerably by simply moving your eye to the next word to complete the sentence. Once you understand what the sentence means you may continue reading or perhaps be stimulated to ask questions or formulate a conclusion based upon what you have read. Two people may read the same sentence, hear the same political speech or see the same photograph but derive completely different meanings and responses (e.g., you may immediately like or dislike something). Similarly, two people may take the same drug and have different qualitative and quantitative responses (this is known as “inter-individual biological variability”). Did you like the effect of the drug or not? Of perhaps more interest to a given individual, there may be variability, and sometimes no response, in the same subject over time (“intra-individual biological variability”). Did your initial response to the drug change over time?

The brain receives, integrates, and responds to outside sensory information from different receptors in peripheral organs (eyes, ears, nose, tongue, skin (Chapter 4). However, the brain is responsible for something even more interesting than responding to external sensory information; it is responsible for cognition. Your brain stores each fact, thought, belief, feeling, and emotion that you have ever experienced. This marvellous feat is performed through changes in the functional activity of cells within the brain. Changes in brain chemistry produced by external environmental stimuli or internal biochemical stimuli are responsible for all behavior, including those biobehavioral changes produced by psychoactive drugs.

How does the brain manage all of this? In part, the answer is in the specialization of the brain and the complexity of its neural connections and communication. In order to appreciate how drug-induced changes in the normal activity of the brain alter behavior, let's first take a look at a simple model of how events in your environment can change behavior and your thinking!

BBB Model of Drug Action

We begin by examining how the brain responds to changes in its environment and introduce the BBB Model of Drug Action. Imagine that you are sitting

8 What Is a Drug?

quietly in a room, relaxing, when suddenly a firecracker or similar device explodes behind you. What happens? If you are like most people, you will probably startle, freeze momentarily, become hyper vigilant for other danger, your pupils will become dilated, the hair on your neck will stand erect, and your heart rate and blood pressure will be elevated. Eventually, when the danger passes, the effect wears off and you return to normal.

The BBB model has three components (see Figure 1.1): a stimulus (S), the event that started everything going (in this case, a loud noise); a



Figure 1.1 BBB model of drug action

sensory receptor system (SRS) for detecting the noise – in this case, the auditory system but perhaps also the visual and tactile (touch) systems; and a response (R). The response consists of activation of many different systems. You may have jumped, been frightened, felt your heart race, your muscles tense, or the hair on the back of your neck stand up. At the very least, your thinking changed. You most likely asked yourself, “What the heck was that?”

Psychoactive drugs work in exactly the same manner. Using the BBB model, the stimulus is not a loud noise but a psychoactive drug. The receptor system is not limited to sensory systems that send auditory, tactile, visual, taste or other information to the brain, but involves receptors located on cells in different parts of the brain. Changes in those brain receptors change the way we think and feel. Let’s think about this model for a moment. Are there any drugs that produce similar behavioral or physiological effects (e.g., increased heart rate, arousal, fear)? Of course there are. If you were thinking of stimulants like cocaine, you would be correct. What if the “stimulus” used in the BBB model was so boring and uninteresting that you fell asleep? Are there any drugs that do that? Naturally there are, and we will be discussing them throughout this book.

The BBB model is not limited to drug use, nor is the brain only affected by drugs. We respond to our environment all the time. Psychoactive drugs change the way we perceive and respond to our environment but by themselves really don’t have any effect. That’s right, our recurrent theme; drugs do not make you high! Psychoactive drugs alter brain chemistry and once that happens, behavior changes. Many things alter brain chemistry, not just drugs. People you meet and whose company you enjoy give you a very different feeling than people who are rude, obnoxious, and “toxic”. Both types of people change your brain chemistry, but in very different ways. Similarly, psychotherapists also change brain chemistry in their patients. As marvelous as many of the current psychotherapeutic medications are, there will never be a drug that is as effective or as specific as a good therapist being there for the patient with an empathetic word or gesture. Even so, the skilled clinician produces changes in brain chemistry in generally the same way as the drug. Therapists and drugs are just different stimuli, but drugs generally have a more dramatic immediate effect in reducing undesirable symptoms to demonstrate how outside events change brain physiology and behavior.

Now let’s take a closer look at the brain, its parts, and how it works (Chapter 2). And for those of you who were wondering, BBB stands for Brick’s

10 What Is a Drug?

Big Bang, named after the teaching model developed to demonstrate how the world around us can change physiology and behavior.

Selected Bibliography

- Erickson, C. K. (2007). *The science of addiction: From neurobiology to treatment*, W.W. Norton, New York.
- Erickson, C. K. (2008). In defense of “dependence”. *Alcoholism: Clinical and Experimental Research* 32: 1–3.
- Kelly, J. F. and Westerhoff, C. M. (2010). Does it matter how we refer to individuals with substance-related conditions? A randomized study of two commonly used terms. *International Journal of Drug Policy* 21: 202–207.
- White, W. and Kelly, J. (2011). Alcohol/Drug/Substance “abuse”: The history and (hopeful) demise of a pernicious label. *Alcoholism Treatment Quarterly* 29: 317–321.

The Brain–Behavior Relationship

2

We continue our journey through several centuries of scientific study that progressively lead to the inescapable conclusion that the brain controls everything the body feels, thinks, and does. Consider the fact that by questioning the brain – behavior relationship, the brain is doing something that no other organ can do – it is evaluating its own existence and purpose! People have not always recognized the awesome power of the brain in affecting behavior, or how the environment affects the brain. In this chapter we set the stage for this process by tracing some of the historically significant research that ultimately became the field of neuroscience and begins to give us a developing picture of “why people take drugs”.

Mind–Body Dichotomy

The relationship between the brain and behavior has fascinated philosophers and scientists for thousands of years. You might say that the brain has captured its own imagination. Even so, for most of that time the brain and behavior were considered separate entities that interacted. It was Aristotle who, more than 2,000 years ago, discussed how and where the soul interacted with the body. For Aristotle the question was, how does our conscious mind (what he called the soul) enter the physical body and what happens to the mind/soul when we die? Descartes (1596–1650), a philosopher, viewed the mind and the body as separate. He believed that the body was simply a robot with biological parts that had “reflex” actions. These actions were the result of animal

spirits that moved through nerve cells and were responsible for transmitting sensory information to the brain. Behavior was the reversal of these reflexes, initiated by the free will of the soul and mediated through the pineal, a small roundish gland located within the brain. These ideas were simplistic and not very accurate, but they did get people thinking about how the brain worked.

The Mind is Physical

It was not until about 1651 that Thomas Hobbes, a colleague of both Descartes and Galileo, began to describe the mind in physical terms. Hobbes relied upon the teachings of another philosopher, Democritus, who several hundred years earlier suggested that the body and all other matter were composed of small objects he called *atomas* (atoms) – a Greek word meaning uncut or indivisible.

By the late seventeenth and early eighteenth centuries, the empirical method of scientific inquiry was formulated. Namely, the empiricists argued that consciousness could be explained in terms of physics and chemistry. Although the empiricists didn't have a clue about how this actually worked, their beliefs were the beginnings of behavioral neuroscience and biological psychology, the scientific studies of the physiological basis of behavior.

One of the many new empiricists was John Locke (1632–1704). Locke believed that experience is a combination of current sensory information and reflection on past sensations. Locke hypothesized that at birth, the mind is like a book full of blank pages. With experience, the pages of the book become filled with information, and associations between information and experience give rise to new ideas. Most importantly, Locke believed these to be physically-based phenomena but provided little insight as to how the associations were physically formed.

Enter the Nervous System

The empirical school of thought continued into the next century and both received and projected great influence through the work of David Hume (1711–1776), a philosopher and historian. In his book, *A Treatise of Human Nature*, Hume suggested that the mind is not just a collection of experiences stored in the brain, as Locke suggested, but is the result of nervous system activity.

The idea that nervous system activity has something to do with behavior was furthered in the 1830s by Johannes Müller (1801–1858), who wrote a highly influential treatise titled *The Handbook of Human Physiology*. In his book, Müller proposed a doctrine of “specific nerve energies”, which stated that the stimulation of a particular nerve would produce a particular sensation. In other words, specific nerves have specific functions. In future chapters, we will learn how psychoactive drugs affect specific nerve functions to alter behavior.

The Bioelectric Brain and Behavior

The first glimpse of the way the brain communicates information to the rest of the body came from studies involving electrical stimulation. Galvani noted in 1791 that when he touched the dissected nerve of a frog’s leg muscle with a rod charged with static electricity, the muscle twitched. Fritsch and Hitzig (1870) used a similar technique to show that low-intensity electrical stimulation on the cortex of the brain produced movement on the opposite side of the body in dogs. They then systematically plotted the location of each cortical electrode site and the corresponding movement and produced the first crude map of the functional activity of the cortex of the brain (Chapter 4). These were among the first studies to demonstrate that the relationship between brain cells and behavior was electrical in nature.

Neurons and Synapses Discovered

Toward the end of the nineteenth century, it became apparent that the electrical connections between nerve cells in the brain are not direct. Santiago Ramón y Cajal (1852–1934), a Spanish neuroanatomist, developed a staining technique for nervous system tissue, proving conclusively that nerve cells do not physically touch but are separated by a small gap. Cajal suggested that nerve impulses pass from one individual brain cell to the next. This was a stunning discovery that changed the way in which we viewed the connectivity of the nervous system. The significance of his discovery is probably best summarized by Cajal himself, who wrote that he “hunted cells with delicate and elegant forms, the mysterious butterflies of the soul, the beatings of whose wings may some day—who knows?—clarify the secret of mental life”.

Cajal’s prophetic view of the importance of nerve cells was fulfilled, in part, by Sir Charles Scott Sherrington (1857–1952), a British physiologist who was the first to study and describe the anatomy of a reflex arc and who coined the term “synapse”. Sherrington also described receptors for food, motion, and sensations that enable organisms to monitor their environment and respond to stimuli.

Evidence of a Brain–Behavior Relationship

Up until now, the understanding of the brain-behavior relationship was mostly limited to motor responses and philosophical musings about the soul and that experiences somehow give rise to thoughts. The relationship between the brain and behavior came into clinical focus in the late 1860s when Paul Broca, an eminent French physician, performed an autopsy on an individual who had been unable to speak for 30 years. Broca found that the patient had a lesion (brain damage) in the third convolution of the left frontal lobe. Based upon this observation and others that followed, Broca concluded that speech is localized in this area on the left side of the brain.

Understanding of the connection between the brain and emotion came at about the same time through the misfortune of Phineas Gage, the foreman of a railroad construction team. Part of Phineas’ job was to use a long tamping rod to push dynamite down a hole that had been drilled into the rock (see Figure 2.1). Unfortunately, in doing so, he inadvertently sparked an explosion that launched the large iron rod out of the hole and through his forehead. Much to everyone’s surprise, Phineas Gage lived, but his personality changed from well-mannered, conscientious and deliberate to irritable and ill-mannered. When he died, many years later, it was found that Gage’s accident had destroyed part of the brain called the limbic system.

The limbic system is involved in many aspects of behavior including emotion and is now also believed to be one of the sites of action for psychoactive drugs. After the Gage accident, no longer was the relationship between the brain and behavior limited to motor functions or robotic reflexes.

One of the most interesting findings in the first half of the twentieth century came from the work of Wilder Penfield, an American neurosurgeon. In the course of his clinical work, Penfield found that stimulating certain brain areas resulted in anatomically specific body movements but also produced “psychic” experiences. Extending our understanding about the brain mechanisms that change behavior, Penfield found that low voltage electrical



Figure 2.1 Phineas Gage

stimulation of regions along the cortex controlled bodily movements (motor outputs) in front of the Fissure of Rolando or central sulcus (see Figure 4.4) and controlled sensations from the skin (sensory inputs) behind it. He also found that damage to the hippocampus, one of the limbic system structures deep within the brain, prevents the storage of new memory traces. Damage to the hippocampus also impairs short-term memory beyond the immediate attention span, although memories formed prior to hippocampal damage are not impaired. Although Penfield worked primarily with a clinical population (e.g., epileptics), his work consolidates the relationship between cognition and subtle electrical activity. Evidence was gathering that the brain controlled emotions and other behaviors including memory.

The Emotional Brain

Walter B. Cannon (1871–1945) was an American physiologist who studied emotion. Up until the early twentieth century, it was believed that visceral

(i.e., organ, glandular) responses created emotions – my heart is beating rapidly, therefore, I must be afraid. Cannon proposed and demonstrated that emotions are not related to visceral responses such as increased heart rate, as contemporary theorists imagined. For Cannon, it was because the brain signaled danger that one became afraid and the heart rate increased. How did this occur? Cannon proposed that one part of the brain, the cortex, normally inhibits another brain structure, the thalamus, from generating certain emotions, such as rage. (We will discuss these structures in more detail in Chapter 4.) When the normal functioning of the cortex changes, it no longer inhibits other brain areas from expressing emotions. Subsequent scientists have expanded the anatomical parts and interpretation of Cannon’s model. For example, in 1937, Papez described a circuit in the brain that activated emotions. The Papez circuit included the cortex, cingulate gyrus, parts of the thalamus and hypothalamus that became the framework for the limbic system. Other scientists of that era included the hippocampus and amygdala as part of the limbic system. Cannon’s initial concept of cortical disinhibition has a useful role in explaining some psychoactive drug effects. Cannon also coined the term “homeostasis” to describe the stability of an organism’s internal environment. Changes in homeostasis are a key part of our present understanding regarding the development of tolerance to the intoxicating effects of drugs, although Cannon himself apparently did not consider this possibility.

The Organization of Behavior

The synthesis of understanding the brain–behavior relationship came into focus with a key publication, *Organization of Behavior* (1949), by D. O. Hebb, a prominent and influential scientist in cognitive neuroscience. Hebb proposed a comprehensive model of how perception, emotion, memories, and other behaviors are produced by physiological and chemical changes within the brain. Fifty years later, and with the advent of techniques like functional magnetic resonance imaging (fMRI), researchers are tracking the encoding and formation of memories in brain regions such as the hippocampus. Each step in the evolution of our understanding of how the brain works has led us closer to understanding the relationship among drugs, the brain, and behavior. This also brings us to the question of why are drugs at all?

Why Do People Take Drugs? The Neural Basis of Drug Use and Addiction

Over the last 40 years, neuroscience has contributed greatly to our understanding of the specific neuropharmacology of psychoactive drugs. In the last 50 years, scientists have become increasingly interested in the question of why people use psychoactive drugs in the first place and what changes occur in the brain to produce behaviors that perpetuate the cycle craving and dependence. The answer to this important question actually began many years ago.

In the 1950s, psychologist James Olds and his graduate student Peter Milner were interested in the effect of brain electrical stimulation on learning and arousal. Since some researchers had demonstrated that stimulation of certain brain areas was aversive, Olds wanted to make sure that the region he was stimulating did not produce aversive effects. Using small stimulating electrodes similar to those used by Penfield, Olds missed his intended target and stimulated another brain area, probably the hypothalamus. When an animal entered a corner and electrical stimulation was applied, the animal quickly learned to stay in that corner (see Figure 2.2). What did this mean?

Olds reasoned that the electrical stimulation produced some kind of a reward because additional studies revealed that animals would work for

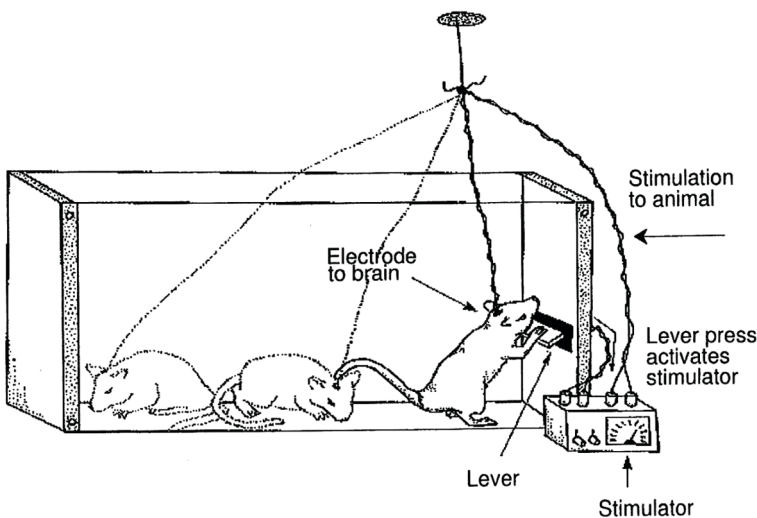


Figure 2.2 Intracranial self-stimulation of reward pathways in the brain

electrical stimulation of areas along the medial forebrain bundle (MFB; See Figure 4.6), a pathway of brain cells that connects various brain areas, including the hypothalamus. In some studies, animals would press a lever hundreds of times an hour or more to receive electrical stimulation of the brain. Some animals would lever press to the exclusion of other activities including eating, drinking water, having sex and playing with littermates. (If you think this sounds something like an addiction, you are correct.) Since then, various models of addiction based on somewhat similar neural substrates of reward have evolved.

Current theories about the reinforcing effects of addictive drugs suggest that the medial forebrain bundle (now more often known as the mesolimbic dopamine system, or MDS) is a key site in the neurobiology of addiction (see Chapter 16). It is believed that drugs release neurochemicals located in the brain cells comprising the MDS. It is the release of a naturally present neurochemical that promotes reward and craving for drugs, and “dysregulation” of these neurochemicals is related to the compulsive overuse of drugs.

Selected Bibliography

- Clark, J. (Ed.) (1984). *The human body: The brain: Mystery of matter and mind*. New York: Torstar Books.
- Clark, J. (Ed.) (1984). *The human body: The nervous system*. New York: Torstar Books.
- Fernandez, G., Effern, A., Grunwald, T., Pezer, N., Lehnertz, K., Dumpelmann, M., Van Roost, D. and Elger, C. (1999). Real-time tracking of memory formation in the human rhinal cortex and hippocampus. *Science* 285: 1582–1585.
- Glickman, S. E. and Schiff, B. B. (1967). A biological theory of reinforcement. *Psychological Reviews*, 74: 81–109.
- Gregory, R. (Ed.) (1987). *The Oxford companion to the mind*. New York: Oxford University Press.
- Hebb, D. O. (1949). *The organization of behavior. A neuropsychological theory*. John Wiley and Sons, Inc., New York.
- Koob, G. F. (1992). Neural mechanisms of drug reinforcement. In: P. Kalivas and H. Samson (Eds.) *The neurobiology of drug and alcohol addiction*, Vol. 654, *Annals of the American Academy of Sciences*, pp. 171–191.
- Koob, G. (2015). The dark side of emotion: The addiction perspective. *European Journal of Pharmacology*, 753: 73–87.

- Müller, J. (1842). *Handbuch der Physiologie des Menschen* [*Handbook of human physiology*] (Vols. 1 and 2). London: Taylor and Walton. (Original work published 1833–1840).
- Nauta, W. and Feirtag, M. (1986). *Fundamental neuroanatomy*. New York: Freeman, p. 309.
- Olds, J. and Milner, P. (1954). Positive reinforcement produced by electrical stimulation of the septal area and other regions of the rat brain. *Journal of Comparative and Physiological Psychology*, 47: pp. 419–427.
- Wise, R. (1990). The role of reward pathways in the development of drug dependence. In: D. Balfour (Ed.) *Psychotropic drugs of abuse*. Elmsford, NY: Pergamon Press.

Pharmacokinetics

3

We are now ready to begin the first part of our journey for a drug to reach its primary target – the brain. In this chapter we trace the path of a drug that affects our brains from the route of administration, to the site of absorption, to how much drug is absorbed into the circulation (bioavailability), to the site of action, and then learn how the drug is biologically altered and leaves the body. A key concept in pharmacology, called pharmacokinetics, helps us understand those factors that most affect the onset, strength, and duration of drug action. In this chapter, we will learn how drugs get to their ultimate destination – the brain.

How Do Drugs Get to the Brain and What Do They Do?

For any drug to have an effect, it must first make its way into the body and enter the blood. *Pharmacokinetics* is the study of the absorption, distribution, metabolism, and excretion of drugs. Pharmacokinetics may be affected by age, gender, disease, individual physiology and drug characteristics determine when and how much drug is available to interact with cells in the brain and elsewhere. Thus, *bioavailability*, defined as how much of the drug eventually gets into the system and is available to interact with target tissue, is an important concept in neuropharmacology. Similarly, unless there is a mechanism to change and/or remove the drug from the body, it will exert its effect forever!

Entering the Circulation: The First Step

There are several means available to move the drug from the outside world into the blood. The main routes of administration are:

- Oral (by mouth)
- Pulmonary (through the lungs)
- Surface absorption (across the mucous membranes)
- Injection (into tissues or veins)

Oral Administration

Oral administration is the most common, and certainly one of the easiest, ways in which drugs enter the body. With few exceptions (discussed later), drugs taken by mouth enter the circulation through the gastrointestinal system. Regardless of whether the drug is a liquid like alcohol or a solid such as a pill, tablet or a psychedelic fungi or food, the route is the same: the drug is swallowed and enters the stomach. Most psychoactive drugs have no effect in the stomach, but the stomach environment can alter the bioavailability of drugs. For example, Tagamet (cimetidine) is a non-psychoactive therapeutic drug used to treat gastric acid reflux (heartburn). Cimetidine inhibits an enzyme called gastric alcohol dehydrogenase (GADH) that breaks down alcohol (see Chapter 10) so more alcohol is available to enter the circulation.

Enzymes, such as alcohol dehydrogenase (ADH), are proteins that enhance biochemical transformations. In other words, enzymes change one biochemical compound to another. As its name suggests, ADH is the enzyme that also oxidizes alcohol. Therefore, the bioavailability of alcohol will be proportionally increased if a person takes cimetidine (which reduces ADH activity) and decreased if a person eats or drinks fructose, a sugar that increases the activity of ADH.

Gastric enzymes may also decrease bioavailability of a drug by destroying the drug while it is still in the stomach. Cocaine and heroin, for example, can produce psychoactive effects when consumed orally, but because these drugs are partially digested in the stomach, bioavailability is low. These examples simply point out that some indirect drug effects that may ultimately alter intoxication occur in the stomach and before the drug enters the circulation.

For the drug taken orally to exert its effect on behavior, it must first get out of the stomach and into the circulation. This process begins as the drug passes from the stomach into the upper portion of the small intestine or ileum. To pass through the small intestine, the drug must be water soluble (easily dissolved in water) and lipid soluble so that it can permeate (pass through) the lipid (fatty) membrane of cells, and move through the walls of the small intestines and into the capillaries (small blood vessels) that surround the intestines. Once the soluble drug has permeated the membranes of the gastrointestinal system and into the capillaries surrounding the gut, the drug is now in the circulation. Lipid and water solubility are not an issue for psychotherapeutic drugs that have been designed to enter the circulation easily. There are some differences in bioavailability among street drugs, however.

Once in the gastric capillaries of the circulatory system, the drug travels through the hepatic portal vein to the liver. From the liver, the circulatory system returns the blood to the heart, where it is then pumped to the lungs, back to the heart, and onward to the rest of the body, including the brain. The entire blood supply makes its way around the body about once a minute and eventually the drug is distributed to every organ and cell in the body (see Figures 3.1 and 3.2).

Drugs taken into the body through the oral route can be affected by the presence or absence of food in the stomach. For most psychoactive drugs taken orally, food slows down absorption and thus bioavailability. Food also does this by slowing movement of food (and alcohol itself) from the stomach to the ileum, the major site of absorption for alcohol.

Advantages of Oral Administration

Oral drug administration is convenient, doesn't require any specialized equipment or training, and provides a relatively rapid onset for solid drugs – about 15 to 30 minutes. The time from the onset of a drug effect to maximum concentration can be significantly different depending on the drug. Less time is usually required if the drug is in liquid form. Also, if the drug is very toxic, purging the remaining drug from the stomach (“pumping the stomach”) will minimize the amount of drug entering the system and its degree of toxicity.

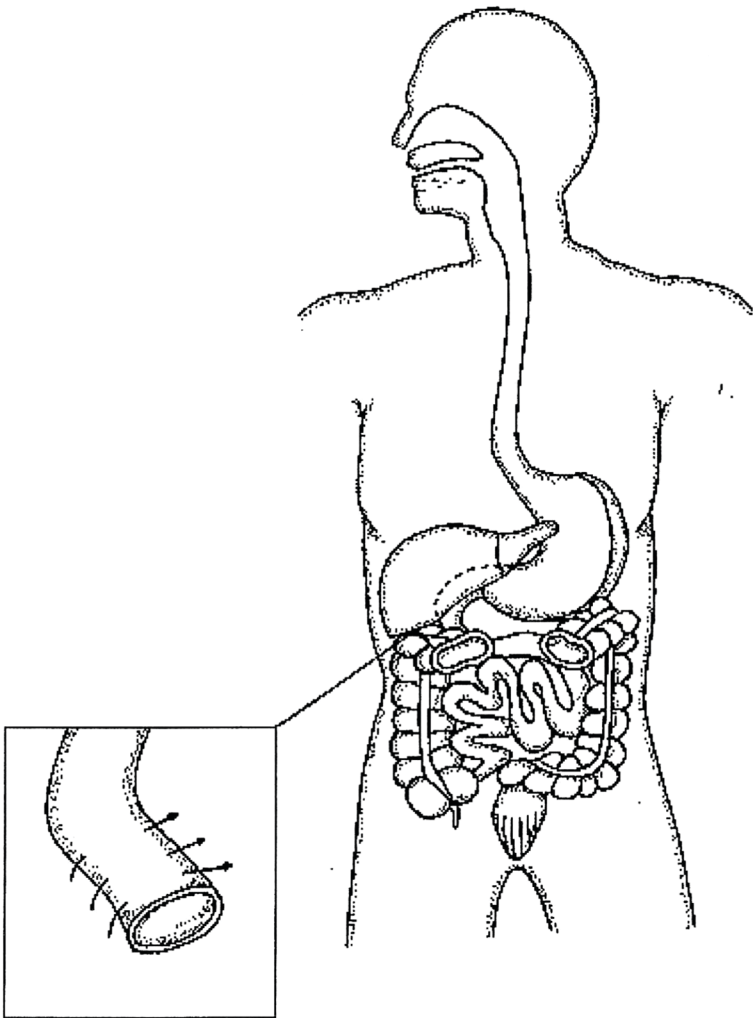


Figure 3.1 Gastrointestinal system. Most psychoactive drugs that are administered orally and that are water soluble and membrane permeable enter the circulation through the upper intestine

Disadvantages of Oral Administration

Despite its advantages and popular use for both therapeutic and nontherapeutic drugs, oral administration is variable and too slowly absorbed to be effective in most emergency situations, such as in reversing overdoses of drugs. It may

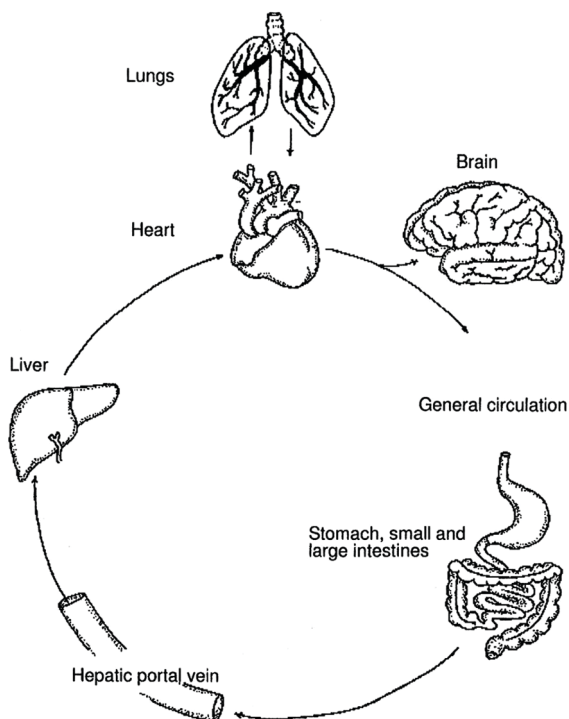


Figure 3.2 From the gastrointestinal system, drugs enter the circulation travelling first to the liver, then continue in the circulation to the rest of the body in a continuous loop

pose administration problems in older or younger patients; for example, some patients may not be able to swallow a large tablet or capsule. If the patient is unconscious, oral administration is not an option and a different more suitable route must be chosen.

Pulmonary Administration

This is the fastest route to get some amount of the drug directly into the circulation. Drugs that are inhaled directly into the lungs, by definition, enter the circulation through the pulmonary system. When tobacco, marijuana, or crack cocaine are smoked, for example, particles of the psychoactive drugs in these compounds (nicotine, THC, and cocaine, respectively), as well as

by-products such as tars and carbon monoxide (CO) become airborne. Other drugs, such as anesthetic gases (e.g., nitrous oxide, halothane) and inhalants (e.g., glue, gasoline, paint thinner, solvents such as toluene) are volatile compounds that mix freely with air and do not require combustion to become airborne.

These compounds enter the lungs and pass through the alveoli (small air sacs that allow the exchange of gases). Volatile or airborne particles pass through the thin membranes of the alveoli and directly into the circulation via the pulmonary artery. Similarly, gases and other volatile compounds already in the blood, such as CO_2 and alcohol, move out of the circulation (through the pulmonary vein) and into the lungs where they are removed (see Figure 3.3).

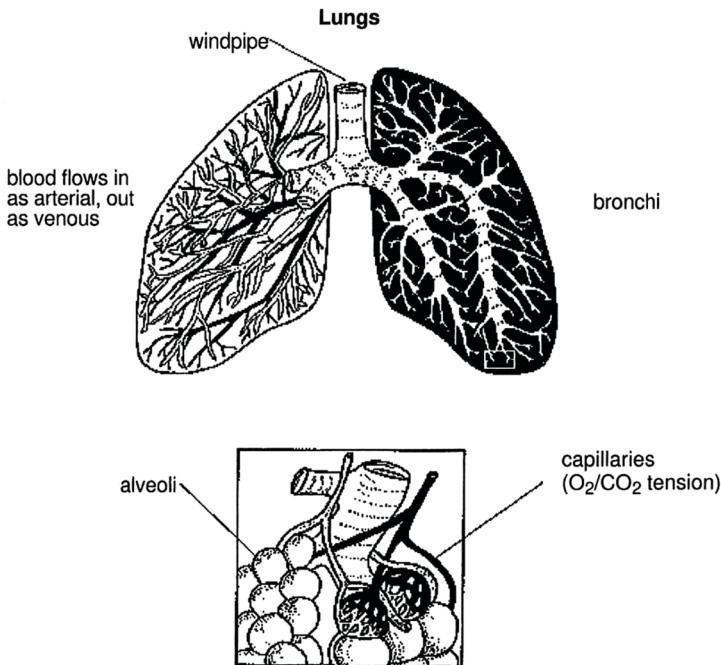


Figure 3.3 The pulmonary system. Capillaries surround the alveoli and exchange oxygen (O_2) for carbon dioxide (CO_2) as gas tensions change. As the lungs expand and fill the alveoli, high levels of CO_2 in the arterial blood pass through the thin membranes of the alveoli. At the same time, O_2 passes out of the alveoli into the venous circulation of the lung

Advantages of Pulmonary Administration

Pulmonary administration has two distinct advantages: (1) it is very rapid – some drug enters the circulation almost instantly, and (2) once the source of the drug is removed, no additional drug enters the body. The latter advantage is important because dose-related escalation of a toxic reaction can quickly be stopped.

Disadvantages of Pulmonary Administration

As with oral administration, the exact dose of the drug that is administered through the lungs is difficult to control, except in a surgical anesthetic environment. Some drug-containing substances, such as marijuana and tobacco, have pernicious side effects including increased risk of pulmonary irritation, emphysema, and lung cancer. Long- and short-term health consequences of solvent and inhalant abuse are only now emerging (see Chapter 12).

Surface Absorption

Psychoactive drugs can be absorbed into the circulation through various mucosal membranes of the mouth or other cavities. Once in contact with mucous membrane or other tissue, soluble drugs can enter nearby capillaries and eventually make their way to the general circulation. The absorption of drugs through tissues in the mouth, nose, etc., is sufficiently different that they are considered separately from absorption through membranes in the gastrointestinal or pulmonary system.

It is a common misconception to believe that drugs such as cocaine are inhaled into the lungs, when in fact cocaine (and other drugs, e.g., heroin, amphetamine) is absorbed via insufflation (commonly termed “snorting”) or sprays (e.g., naloxone for opioid overdose) into the posterior nasal membrane, where it is absorbed into the circulation (see Chapter 7). Nitroglycerin, a cardiac medication, and nicotine from chewing tobacco and cigars are absorbed through the membranes of the mouth (e.g., sublingual). Other forms of absorption include: through the skin (transdermal) as in the use of a Nicoderm patch, a smoking cessation medication, or a Dramamine patch for seasickness; Trusopt, a glaucoma medication applied to the cornea of the eye (transcorneal); and in rare instances through the rectum (alcohol enema).

Almost any method a drug abuser can think of when desperate (e.g., rectally, vaginally, eyes, ears) has been used with legal and illegal drugs. Often these other sites are used (with relatively low effectiveness) for recreational purposes, or to avoid detection of use through the usual sites of administration that may prove harmful.

Advantages of Surface Absorption

Drugs administered by absorption slowly enter the circulation at a relatively even rate. The use of a properly designed transdermal patch, for example, can allow small quantities of the drug to be administered over long periods of time, such as a day or more.

Disadvantages of Surface Absorption

Relatively few drugs can be effectively absorbed through the skin or mucous membranes, and those that are will usually enter the circulation slowly. Also, the dose administered is not always equal to the amount of drug that is eventually absorbed into the circulation.

Injection

Water-soluble drugs can be mixed into a solution and injected through a syringe directly into the blood, skin, muscle, or under the skin. The four types of injection are the following:

1. *Intravenous*: the drug is injected directly into a vein. This is the fastest method of administering the total dose of any drug. The onset of effects occurs very rapidly—less than twenty seconds following intravenous (IV) administration. Anesthetics such as pentothal (“truth serum”) or propofol are administered this way as are most local anesthetics and some drugs of abuse (e.g., most commonly, opioids, stimulants).
2. *Intradermal*: the drug is injected between and within the layers of the skin. Tuberculin skin tests are given this way.
3. *Intramuscular*: the drug is injected into a large muscle such as the gluteus maximus (buttocks), triceps or thigh. Intramuscular (IM) administration

places the drug in close contact with rich network blood vessels supplying the muscle tissue. Haloperidol (Haldol), an antipsychotic drug, is administered this way, as are many common medications.

4. *Subcutaneous*: the drug is injected under the layers of the skin and is slowly absorbed into the underlying muscle's blood circulation. Subcutaneous (SC) administration is also known as "skin-popping". Heparin, an anti-coagulant drug, is administered this way.

Advantages of Injection

For most drugs, injection provides rapid onset with a precise dose, especially with intravenous administration. Some drugs are given intramuscularly to prolong their duration of action (e.g., some forms of insulin, a hormone used to treat diabetes).

Disadvantages of Injection

Special equipment is needed and injection methods can be potentially dangerous if sterility of syringes and the injection sites are not maintained (e.g., spreading hepatitis, AIDS). If a toxic reaction develops immediately, the drug's action cannot be stopped. Finally, for some people, injections are painful and sometimes leave a small bruise.

Distribution: The Second Step

What Happens After the Drug Enters the Circulation?

We have now moved the drug from the outside world – from the syringe, medicine bottle, glycine envelope, plastic baggie, bottle etc. – into the circulation. When psychoactive drugs enter the circulation, they are distributed through the blood to the fatty and watery portions of the body. Drugs that are lipophilic (fat-seeking, such as cannabinoids in marijuana) will tend to accumulate in fatty tissues of the body. Drugs that are hydrophilic (water-seeking, such as alcohol) will concentrate in blood and muscle. Differences in body size, gender, age, and height will affect the amount of total body water (TBW) available for the hydrophilic drug to be distributed. This is also

called the apparent volume of distribution (Vd). On average, men are larger and have more muscle mass and therefore more body water per pound than women because muscle cells contain more water than fat cells. Thus, on average, a man will have lower concentrations of drugs in his blood than a woman, even if they are given the same dose and weigh the same. That relationship may change if the woman is a world-class athlete, for example, and the man is a couch potato!

The Vd is necessary to perform pharmacokinetic calculations to answer questions such as how much drug was taken or how much drug will be in the blood if you ingest a known amount. The Vd for various drugs is represented by the equation:

Equation 3.1.

$$Vd = D/C$$

Where D is the dose of the drug and C is the measured concentration of the drug in the blood. The Vd varies with the ability of the drug to bind to plasma protein or tissues, and the affinity to lipids or lipophilicity (pKa) of the drug. Most psychoactive drugs are lipophilic (“fat-seeking”) and have a high Vd (>1.0) whereas drugs that are hydrophilic (distribute well in water) such as alcohol have a low Vd (<1.0). Drugs like acetylsalicylic acid (aspirin) and acetaminophen (Tylenol®) are bound to proteins and also have a low Vd (<1.0). If a drug is bound to proteins it cannot leave the circulation because the drug-protein complex is too large to pass through the blood–brain barrier (described below). Generally, only unbound or “free” drugs can leave the circulation to interact with receptors in the brain.

Knowing the Vd of a drug is useful in performing pharmacological calculations to determine the dose of drug taken (if you know the blood concentration) or the drug level after ingestion of a known dose. Alcohol, even with its low Vd, freely enters the brain. These are useful in scientific and medical research and have forensic applications as well (see Chapter 18).

Even at this point, where the drug has entered the circulation and has been distributed throughout the body water, psychoactive drugs have no effect on behavior. Regardless of the type or amount of drug, it cannot change behavior unless it makes contact with brain cells. To accomplish this, it must now leave the circulation to come into contact with brain cells. Psychoactive drugs have no effect unless they interact with brain cells (Chapter 5). Although drugs can exit capillaries almost as easily as they enter them, capillaries near the

brain are different because they are surrounded by special cells that form the “blood–brain barrier.”

Blood–Brain Barrier

The blood–brain barrier acts to keep certain drugs and other compounds in the circulation and away from the brain. The blood–brain barrier does this by decreasing the permeability (ability of substances to pass through) of capillaries surrounding and throughout the brain. It is the reduction in permeability of capillaries that results in this selective barrier. This change in permeability occurs because the blood–brain barrier only allows drugs of a specific molecular size or those that are bound to special transport proteins to pass through capillary walls to the brain. Compounds that are too large or not fat soluble do not pass through the blood–brain barrier which includes a unique arrangement between capillaries and cells called astrocytes; the capillaries are surrounded by astrocyte cells so that the permeability of the blood vessel is restricted (see Figure 3.4). Although this barrier protects the brain

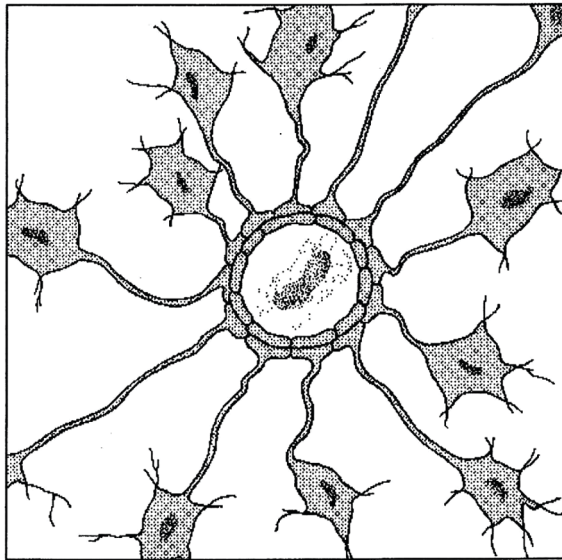


Figure 3.4 Cross-sectional view of cells surrounding a capillary in the brain to form the blood–brain barrier

from various infections (so that we do not become delirious every time we get the flu), most psychoactive drugs readily pass through. Obviously, all drugs that produce changes in behavior pass through the blood–brain barrier.

The transport of drugs from the blood into the brain is not automatic and is affected by numerous factors including transport proteins and diet. Diet can be significant since some foods contain amino acids and carbohydrates that may decrease the uptake of certain drugs because they compete for the same proteins to transport them into the brain. Some medications (high doses of acetaminophen) may alter brain permeability.

Elimination: The Third Step

Drugs are eventually metabolized and eliminated from the body. Individuals would remain under the influence of a drug indefinitely were it not for metabolism and elimination. Small amounts of the unchanged drug can be eliminated through the skin, breath, or urine, but most drugs are changed by enzymes through a process of oxidative metabolism. Enzymes are proteins that are secreted from cells and act as catalysts to produce a chemical change in other substances. Enzymes are present in the blood as well as the liver, lungs, stomach and other organs. However, most psychoactive drugs are altered by liver enzymes or by enzymes in the blood. In the case of alcohol, some metabolism may occur in the stomach. Blood flows through the liver as it makes its way through the body (Figure 3.2). The liver which is a triangular organ is positioned mostly on the right side of the abdominal cavity. Small amounts of drug in the circulation are metabolized (broken down) with each pass through the liver.

The metabolism of fat-soluble drugs results in the formation of water-soluble metabolites that can pass through the kidneys and be excreted in the urine. The kidneys, bean-shaped organs about the size of your fist located in the rear abdominal cavity below the ribs, remove waste products through their primary cellular unit, the nephron. The nephron filters the blood, allowing unwanted substances (e.g., water-soluble metabolites) to enter the bladder, where they are then excreted in the urine.

Drug Half-life

In clinical practice, maintaining a therapeutic drug level, knowing when to re-administer the drug, and being able to predict when the action of the drug

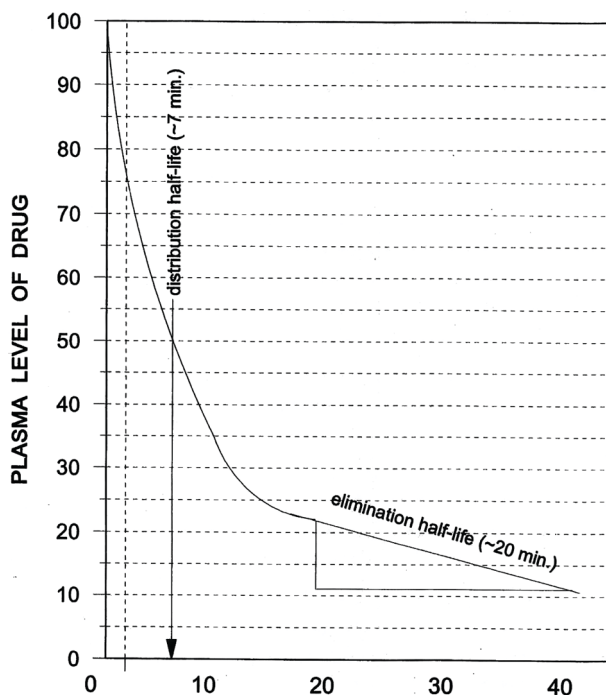


Figure 3.5 The amount of time required to reduce the initial peak by one-half defines the distribution half-life

will stop are important concepts in neuropharmacology. The term “half-life” is used to describe the relationship between the concentration of drug in the blood and time. The time course of most drugs can be described by their distribution or elimination half-life.

The distribution half-life is the amount of time required for the initial peak level in tissues (typically blood) to be reduced by 50 percent. The relationship between these half-lives is illustrated in Figure 3.5. It can be seen that the concentration of an intravenously injected drug increases rapidly, reaching a peak almost immediately. The blood concentration first decreases rapidly, then more slowly. The rapid decrease is due to the distribution of the drug throughout the body water and fat.

The elimination half-life is the amount of time required for the drug concentration to decrease by 50 percent in blood once the distribution half-life is complete. Table 3.1 shows that, regardless of the initial drug concentration seven half-lives later, the concentration will be close to zero.

Table 3.1 Relation of Half Life to Drug Concentration

Post-absorption concentration (mg/L)	Number of half-lives	% of drug eliminated	% Remaining
20	0	0.00	100.00
10	1	50.00	50.00
5	2	75.00	25.00
2.5	3	87.50	12.50
1.25	4	93.75	6.625
0.625	5	96.875	3.125
0.313	6	98.437	1.563
0.156	7	99.247	0.753
0.781	8	99.623	0.377

The slower decline in blood concentration represents primarily metabolic elimination. In the example given, distribution half-life is about seven minutes and the elimination half-life is about 20 minutes, since that is the amount of time required for blood concentration to decrease by half (i.e., 50 percent). Generally, most drugs are completely changed or eliminated from the body in about seven half-lives. For example, if a drug has a known half-life of 24 hours and a measured concentration of 20 mg/L, it will take approximately a week for the drug to be completely eliminated from the circulation. Depending on the method of testing, that drug would be detected in blood for at least 4–5 days after use.

Applying Pharmacokinetics: The Relationship Between Dose and Effect

How Much Drug is Needed? The Dose–Response Curve

The effectiveness of a drug in a given population and at various doses can be determined by establishing a dose–response curve. Dose–response curves show the potency, slope, efficacy and dose required to produce the maximum effect.

The dose of a drug, coupled with the V_d of the subject, rate of elimination or half-life, and time of administration can be used to estimate the concentration of drug in blood, as illustrated in Figure 3.5. Such analyses have many applications including determination of how much of the drug is necessary

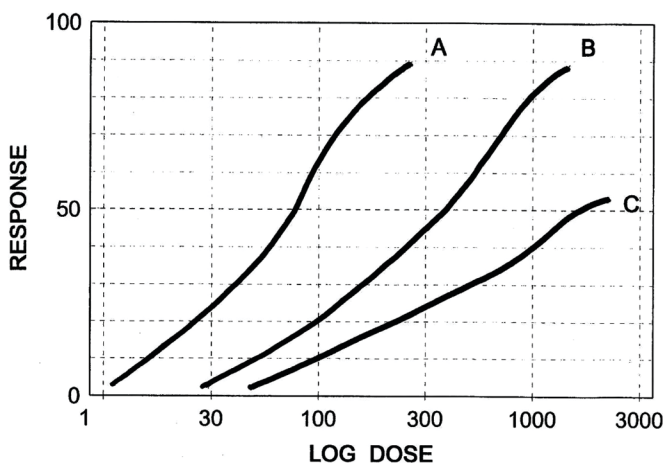


Figure 3.6 Drug potency

to produce a response. This is referred to as the drug *potency*. For example, in Figure 3.6, Drug B is more potent than Drug C because it only requires one-tenth the dose to produce the same effect. This might lead you to believe that Drug B is somewhat better than Drug C 50 percent of the time because less is required. Actually, just the opposite is probably true. Although Drug B is more potent, it is probably also more toxic. Small errors in dosage of a highly potent drug with harmful effects (e.g., morphine) can be disastrous especially when combined with potentially harmful chemicals, diluting or “cutting” agents. “Bathtub chemists” working hastily to manufacture cheap, illicit psychoactive drugs in clandestine “laboratories” are working to make a profit, not to protect the consumer.

The slope of the dose–response curve refers to the linear (straight line) portion of the curve, rather than the curvilinear (curving line) section. Drugs with a steep slope on the dose–response curve may have a narrow margin of safety. That is, small differences in the dose will produce large differences in the effect. Drug A (see Figure 3.6) has a narrow margin of safety compared to Drugs B and C.

Drug Efficacy

Drug *efficacy* refers to the maximum effect of the drug, regardless of how much drug is administered (or how much drug is present at the cellular site

of action). For example, although the caffeine extracted from the coffee bean and the cocaine extracted from the coca plant are both stimulants, you will never get the same intensity of effect from drinking coffee that you will from cocaine, no matter how much coffee you drink. Therefore, cocaine has greater efficacy than caffeine.

Lethal Dose, Effective Dose and Therapeutic Index

Most *psychoactive* drugs are toxic in high doses. The lethal dose at which 50 percent of the population would be expected to die from the dose is called the lethal dose 50 (LD_{50}). Some psychoactive drugs, such as alcohol, have a relatively low LD_{50} . Others such as LSD and marijuana have a very high LD_{50} . Most *psychotherapeutic* drugs have a very high LD_{50} . The dose that is effective in producing a therapeutic response in half the population is called the ED_{50} . Ideally, therapeutic drugs will have a low effective dose (ED) and a high LD_{50} .

The ratio of LD to ED_{50} is referred to as the *therapeutic index*. The therapeutic index of a drug tells you about the safety margin between effectiveness and toxicity. The higher the therapeutic index, the safer the drug.

Drug Interactions

A drug interaction may occur when two or more drugs are combined. There are two basic types of drug interactions: *pharmacokinetic* and *pharmacodynamic*. The behavioral outcomes of some interactions are often difficult to predict, particularly when more than one type of interaction takes place or when multiple drugs with different effects are combined.

Pharmacokinetic

Pharmacokinetic drug interactions involve changes in the bioavailability of the drug. Changes in absorption, distribution, or metabolism affect how much drug reaches receptors in the brain or elsewhere (see Table 3.2).

Increases or decreases in *drug absorption* affect the amount of drug that enters the circulation. For example, alcohol increases the absorption rate of

drugs like benzodiazepines so more drug will enter the blood supply when alcohol is also in the stomach.

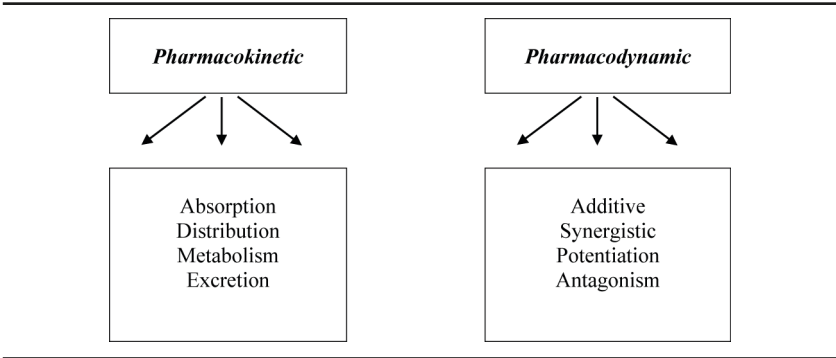
After absorption from the gastrointestinal tract into the circulation, drugs may interact through changes in the *volume of distribution*. Decreases in the volume of distribution will increase drug concentration and vice-versa. For example, alcohol increases the volume of distribution of cocaine, which may thus decrease the concentration of cocaine, thereby decreasing its bioavailability and effectiveness.

Pharmacokinetic changes related to metabolism may also affect drug concentrations. For example, the metabolism of many drugs occurs through shared enzymes. When two drugs share the same metabolic pathway, one drug can alter the bioavailability of the other by competing for shared enzymes. For example, Tagamet (cimetidine, mentioned earlier) and Zantac (ranitidine) are medications called H₂ blockers that interact with alcohol to change its bioavailability through a pharmacokinetic mechanism.

Pharmacodynamic

Pharmacodynamic drug interactions involve changes in the functional activity (for example) of receptors or neurochemicals in the brain. Changes in drug pharmacodynamics can affect the functional activity of brain cells leading to changes in behavior. There are four major pharmacodynamic drug interactions; additive, synergistic, potentiation and antagonistic (Table 3.2).

Table 3.2 Pharmacological Bases of Drug Interactions



Pharmacodynamic Interactions

For the psychoactive drugs described, the mechanism of their action is the alteration of the functional activity of receptors or neurotransmitters in the brain. Some drugs not discussed exert similar effects outside the central nervous system (e.g., cardiac beta-receptor antagonists). Changes in the pharmacodynamics or functional activity of neurons that modulate cognitive and psychomotor effects, for example, will alter physiology and behavior.

Additive

A simple additive drug interaction is when the sum of the effect of two drugs is equal to the sum of the effect of each drug (e.g., $2 + 2 = 4$). For example, benzodiazepines and barbiturates have additive effects and both have additive effects with alcohol. Alcohol also has additive effects with some tricyclic antidepressants such as the amitriptyline (Elavil) but not with other antidepressants. For example, fluoxetine (Prozac) a widely prescribed serotonin reuptake inhibitor does not significantly interact with alcohol.

Synergistic

A synergistic interaction is when the combination of two drugs produces an effect that is greater than the effect of either drug combined (e.g., $2 + 2 = 6$). Synergistic interactions produce effects far greater than would be predicted from an additive interaction. For example, alcohol and carbon tetrachloride, a cleaning fluid, are toxic to the liver. However, the combination of the two produces much more liver damage than would be predicted from the sum of their individual effects. Similarly in some cases alcohol synergistically enhances the sedative effect of barbiturates and some effects of opiates.

Potentiation

Potentiated drug effects are like synergistic interactions but usually describe an increase in the toxic effect of a drug when combined with a non-toxic drug (e.g., $0 + 1 = 2$). For example, Histamine₂ (H₂) antagonists such as cimetidine (used to treat gastric ulcers) can potentiate the effects of alcohol by increasing

the amount of alcohol entering the circulation from the gastrointestinal system because of decreased gastric metabolism.

Antagonism

An antagonistic interaction is when one drug that blocks the effect of another drug (e.g., $2 + 2 = 1$ or $2 + 2 = 0$). Antagonists are very specific. For example, naloxone (Narcan) is used to treat heroin overdose. It works because naloxone has a much higher affinity for opiate receptors than heroin and when given to an overdose patient, there is a rapid reversal of the depression caused by the opioid.

Pharmacokinetic or pharmacodynamic drug interactions potentially occur between thousands of medications. With few exceptions, depressant drugs will exacerbate the depressant effects when combined with other depressants and stimulants will exacerbate the effects of other stimulants when both are taken during the same period. Those interactions may be pharmacokinetic or pharmacodynamic in nature. Also, with few exceptions, combining a depressant and a stimulant does not result in no drug effect or because one “cancels out” the other. For example, the combination of heroin or other opioid and cocaine or another stimulant, a practice known as speed-balling, results in an intense rush for the user. In this book we will focus on the interaction between alcohol, one of the most widely used psychoactive drugs on earth, and other abused (as well as common) over the counter (OTC) medications.

The potential additive, potentiated, or antagonistic interaction of drugs should always be considered in interpreting both toxicology and biobehavioral effects of drug combinations. Alcohol is by far the drug most often detected and involved in accidents, crimes, and various other areas of potential forensic interest. Although the interaction between alcohol and other drugs is beyond the scope of this book, reviews of such interactions are available. Generally, the combination of alcohol with other central nervous system depressants increases the depressant effects. In other instances, alcohol may interfere with the bioavailability of co-administered medications, thereby reducing the effects of the medication.

Now that we have moved the drug from the outside world into the circulation, the following chapters will explore where and how drugs act to change behavior.

Selected Bibliography

- Benet, L., Mitchell, J. and Sheiner, L. (1990). Pharmacokinetics: The dynamics of drug absorption, distribution and elimination. In: L. Goodman and A. Gilman (Eds.) *The pharmacological basis of therapeutics*. New York: McGraw-Hill, pp. 3–32.
- Brick, J. (1987). *Drugs and the brain. An introduction to neuropharmacology*. New Brunswick, NJ: Rutgers University Center of Alcohol Studies.
- Brick, J. (2006). Standardization of alcohol calculations in research. *Alcoholism: Clinical and Experimental Research*, 30(8): 1276–1287.
- Degenhardt, L., Chiu, W-T., Sampson, N., Kessler, R. C., Anthony, J. C., Angermeyer, M., Bruffaerts, R., de Girolamo, G., Gureje, O., Huang, Y., Karam, A., Kostyuchenko, S.⁰, Lepine, J. P.¹, Medina Mora, M. E., Neumark, Y. Ormel, J. H., Pinto-Meza, A., Posada-Villa, J., Stein, D. S., Takeshima, T. and Wells, J. E. (2008). Toward a global view of alcohol, tobacco, cannabis, and cocaine use: Findings from the WHO World Mental Health Surveys. *PLoS Medicine*, 5(7): 1–14.
- Kaufman, M., Chiu, T-M., Mendelson, J., Woods, B., Mello, N., Lukas, S., Fivel, P., and Wighton, L. (1994). In vivo proton magnetic resonance spectroscopy of alcohol in rhesus monkey brain. *Magnetic Resonance Imaging*, 12(8). Elsevier Science Ltd, pp. 1245–1253.
- Kaufman, M., Chiu, T-M., Mendelson, J., Woods, B., Teoh, S., Eros-Sarnyai, M., Mercer, G., and Mello, N. (1996). Brain alcohol detectability increase with repeated administration in humans: A proton spectroscopy study. *Magnetic Resonance in Medicine*, pp. 435–440.
- O'Malley, P. and Johnston, L. (2007). Drugs and driving by American high school seniors 2001–2006. *Journal of Studies on Alcohol and Drugs*, 68: 834–842.
- Watson, P. (1989). Total body water and blood alcohol levels: Updating the fundamentals. In: K. Crow and R. Batt (Eds.) *Human metabolism of alcohol*, Vol. 1, Boca Raton, FL: CRC Press, pp. 41–58.
- Yang, J., Betterton, R., Williams, E., Stanton, J., Reddell, E., Olbonnaaya, C., Dorn, E., Davis, T., Lockhead, J., and Ronaldson, P. (2022). High-dose acetaminophen alters the integrity of the blood brain barrier and leads to increased uptake of cocaine in rats. *Pharmaceutics*, 14(5): 945. Doi:10.3390/pharmaceutics 14050949

Functional Neuroanatomy: Where Do Psychoactive Drugs Act?

Since psychoactive drugs affect the brain to produce their actions, it is important to understand the functions of the various parts of the brain where these drugs act. It is even more exciting to understand that there are separate brain areas for each movement we make, and each thought, feeling, or sensation we have. Despite these distinctions, the brain is highly interactive with each of its parts, creating an infinite number of movement and feeling possibilities, which makes no two people alike in the history of the world.

Neuroanatomy describes the spatial relationships among neural systems, and the underlying components of which formulate sensation, cognition (thinking), emotions and behavior. In this and the next chapter we will set the stage for where and how psychoactive and psychotherapeutic drugs exert their effects.

Since psychoactive drugs affect behavior by changing the nervous system, a review of the overall structure and function of the nervous system is in order. There are two basic “parts” of the nervous system: the central nervous system (CNS) and the peripheral nervous system (PNS). Although anatomically separate systems, the CNS and PNS interact. The CNS consists of the brain, which is responsible for thinking and purposeful behavior, and the spinal cord which sends commands from the brain downstream (Efferent signals) to muscles, organs, and glands and is a conduit for sensory-motor information going upstream from sensory organs to the brain (Afferent signals), where it is processed. Everything outside the brain and spinal cord is part of the peripheral nervous system.

The PNS consists of two branches: the somatic and the autonomic nervous systems. The somatic nervous system interacts with the outside world and controls mostly voluntary movement (e.g., skeletal muscles that are under conscious control), carrying afferent sensory information to the brain and sending efferent command signals from the CNS to muscles. The autonomic nervous system controls involuntary smooth muscles, cardiac muscles and glands and regulates and maintains homeostasis (steady state of temperature, oxygen, fluids, food/energy supplies, etc.) of the internal environment. The autonomic nervous system is further divided into the sympathetic and parasympathetic systems. Most of the time, the sympathetic and parasympathetic nervous systems work in opposite directions. For example, during stress, the sympathetic nervous system arouses the body, causes pupil dilation and peripheral blood vessel constriction, shuts down digestion, increases heart rate, and prepares the body for fight or to take flight, whereas the parasympathetic nervous system has the opposite effect. Most organs have both sympathetic and parasympathetic inputs. Some sensory information (e.g., vision, hearing, smell) goes directly to the brain through one of twelve cranial nerves, which are also part of the PNS.

Psychoactive drugs exert their effects through the CNS but some medications (e.g., blood pressure medications) act directly on the PNS. The basic functional components of the nervous system are illustrated in Figure 4.1.

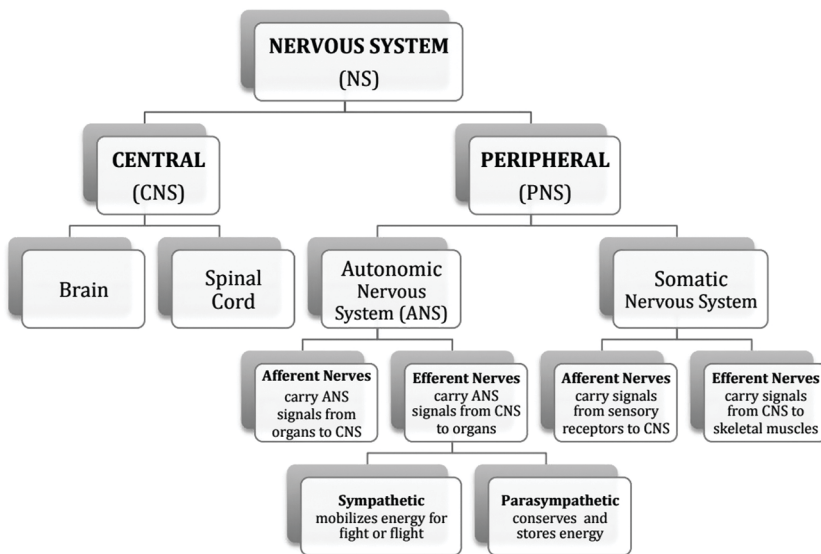


Figure 4.1 Organization of the nervous system

The Brain is the Target of Psychoactive Drugs

Psychoactive drugs change various cognitive (thinking) and motor (movement-controlling) functions by altering the activity of specialized cells within the cortex, cerebellum, midbrain and other subcortical structures. Learning the basic functional anatomy of the brain is helpful in understanding how and where psychoactive drugs exert their effects on behavior.

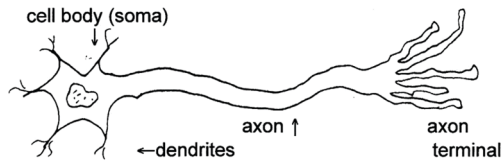
The adult human brain weighs about 1600 grams or about 3½ pounds. The brain is composed of just under 100 billion specialized nerve cells, called neurons and about an equal number of another type of brain cells called glia. These estimates are lower than previously believed but made more complicated because the density of cells varies among brain regions. It is estimated that the number of neurons alone is about the same as the number of stars in the Milky Way! Some of the neurons come together in groups called nuclei (not to be confused with cell nuclei which have specific functions within the cell). Nuclei have distinct anatomical features and specialized functions. There are different classes of neurons based on the structure (Figure 4.2). Some neurons have long axons that form bands or fiber tracts that interconnect nuclei (see Figure 4.2). These can range in length from hundredths of inches inside the brain to several feet in the case of sensory motor neurons outside the brain. Let's get oriented before we begin, since neuroanatomy has its own set of directional terms. Some of these terms will also be helpful in future chapters (see Table 4.1 and Figure 4.3).

Cortex

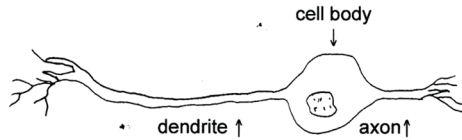
Even casual inspection of the brain reveals a wealth of distinct anatomical features. The most imposing structure is the cerebral cortex, a large convoluted structure that forms the front and uppermost portion of the brain. The cortex has left and right halves. These are referred to as "hemispheres". The hemispheres are interconnected by a band of fibers called the corpus callosum, which passes information between the two hemispheres. Damage to the corpus callosum, which may occur in fetal alcohol syndrome or following certain types of surgery or injury, often results in behavioral and motor abnormalities.

The outer mantle of the cerebral hemispheres is convoluted with deep sulci (grooves) separating gyri (ridges). Dogs, cats, rabbits, humans and other

Multipolar neurons have one axon and multiple dendrites. Their axons are commonly found on motor neurons and interneurons.



Bipolar neurons have one axon and one dendrite extending from the cell body. Such neurons are found in the inner ear and eye, for example.



Unipolar neurons are commonly found in sensory systems where the dendrites are located at the sensory receptor and the axons extend to the spinal cord or brain.

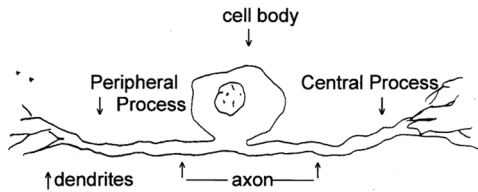


Figure 4.2 Basic classification of neuron based on structure

primates have convoluted cortices, but not all species do. Birds, rats and reptiles have smooth cortices. The dramatic convolutions of the brain are an efficient means of increasing the surface area of the cortex without undue increases in cranial size. This increase in surface area enables a larger number of cells to occupy the same overall space. The cerebral cortex, a thin layer of grey matter, covers the cerebral hemispheres. It has been estimated that if the surface of the cortex were unfolded it would cover more than two square meters! The different types of cells that make up the cerebral cortex regulate a number of sensory, motor and cognitive functions.

What Does the Cortex Do?

Functional neuroanatomy is the study of the relationship between brain structures and behaviors. The six cellular layers that make up the cerebral cortex form a mosaic of anatomically different sensory (input) and motor (output) cells that perform a number of sensory, motor and cognitive functions; muscle and sensory

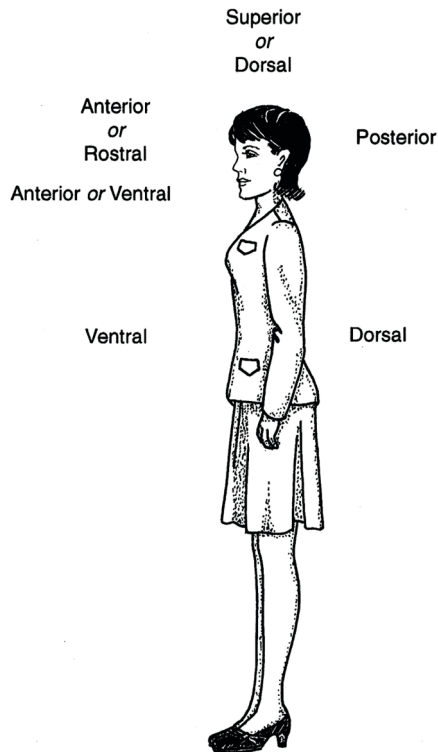


Figure 4.3 Anatomical terms for spatial orientation

Table 4.1 Spatial Neuroanatomical Terms

-
- Anterior/Rostral – toward the front of the head
 - Posterior – toward the back of the head
 - Caudal – toward the feet (or tail, in animals)
 - Superior/Dorsal – toward the top of the head or body
 - Ventral – away from the back of the head or body (belly-side)
 - Medial – toward the middle
 - Lateral – toward the side
 - Pre – before
 - Post – after
 - Afferent – going toward the brain
 - Efferent – going away from the brain
-

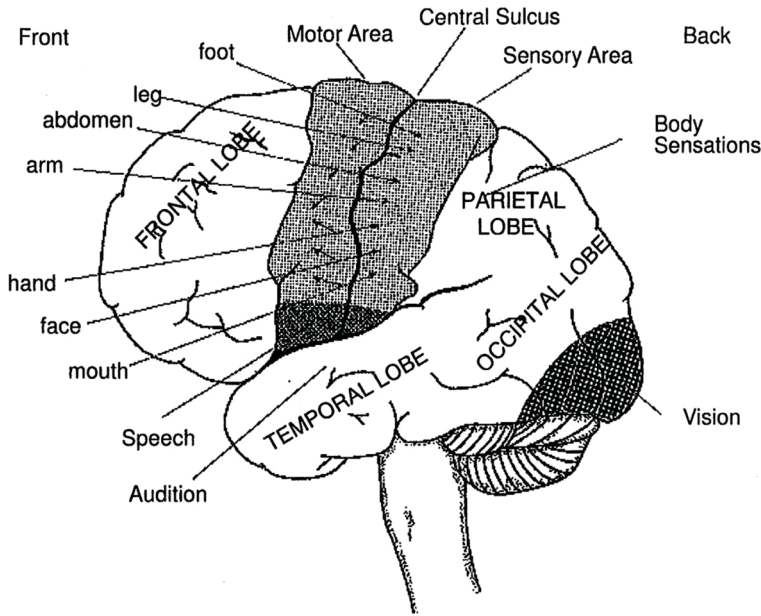


Figure 4.4 Functional anatomy of the cortex

inputs from one side of the body go to the opposite side of the cortex. Similarly, sensory-motor afferent signals from the left side of the brain go to the right side of the body, etc. Surrounding the primary sensory and motor areas are the association areas. Additional association areas are found in the frontal lobes of the cortex, but here there are few, if any, sensory or motor-related cells. Finally, some areas of the cortex are specifically tuned for particular functions (e.g., speech, spatial relationship detection) and are asymmetrically represented (i.e., they occur on one side of the brain but not the other). The functional anatomy of the cortex is depicted in Figure 4.4.

Subcortical Structures

Below the cortex (subcortical) are numerous structures, including the thalamus, hypothalamus, septum, and other groups of cells that form the limbic system. Some of these structures are illustrated in Figures 4.5–4.7.

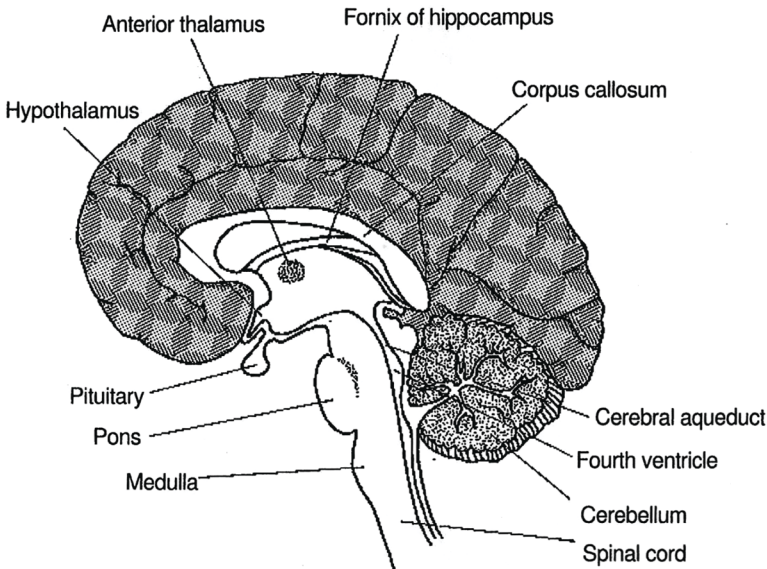


Figure 4.5 Sagittal (mid-slice) view of the brain, illustrating subcortical structures

Cerebellum

The cerebellum is another prominent structure of the brain (see Figures 4.5 and 4.6). It has a multilayered appearance and a number of deeper nuclei. The cerebellum is richly innervated (connected by nerves) with sensory cells, and acts as an anatomical way station, modulating information sent from the cortex down the spinal cord and from the spinal cord back to the cortex. The cerebellum is responsible for coordinating the timing and smoothing out of various muscle movements. Lesions or drug-induced alterations in the cerebellum result in ataxia (impaired muscle coordination) and other impairments.

Brainstem (Midbrain, Pons, Medulla)

The brainstem connects the brain with the spinal cord. The upper part of the brainstem contains the midbrain, pons and medulla. The midbrain is the most dorsal area of the brainstem (see Figure 4.6). The midbrain is positioned above the pons, receives visual information, regulates eye movement and processes auditory information. It also regulates muscle movement.

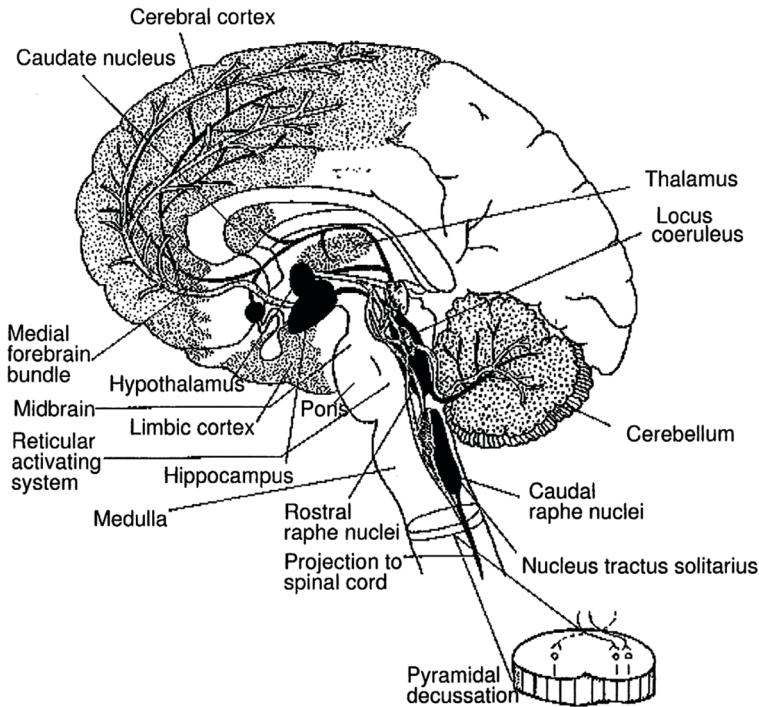


Figure 4.6 Pathways and structures of the brain

The pons contains a number of important nuclei including (1) the reticular formation (also called reticular activating system, RAS), which plays an important role in the sleep/waking cycle and motor control, (2) the locus coeruleus, which supplies most of the brain's norepinephrine, a neurochemical transmitter (see Chapter 5) and (3) the raphe nuclei, another complex of nuclei that supply the neurotransmitter serotonin to many brain regions involved in sleep, pain, aggression, and other behaviors (including mental illness). In addition, the pons contains a number of crossing fibers of the descending (efferent) motor system, most notably the pyramidal decussation (see Figure 4.6). It is here that neurons cross from one side of the brain to the opposite side of the body.

Medulla

The most caudal division of the brainstem is the medulla (Figures 4.5 and 4.6). Below the medulla is the spinal cord. The transition from spinal cord to

medulla is not sharp but is marked by the opening of the central canal into the fourth cerebral ventricle and the absence of spinal nerves. The gray matter of the spinal cord first loses its butterfly appearance and then disappears entirely, giving way to medullary nuclei.

A prominent feature of the medulla is the decussation (crossing over from one hemisphere to the other) of the corticospinal tracts of the motor cortex before their descent through the lateral cortico-spinal tract. It is because of this crossover that damage to one side of the brain may result in sensory-motor impairment on the opposite side of the body. Portions of the medulla also contain specialized cells that control, among other things, the vomit reflex – which is activated when a toxin is detected (e.g., high levels of alcohol).

Thalamus

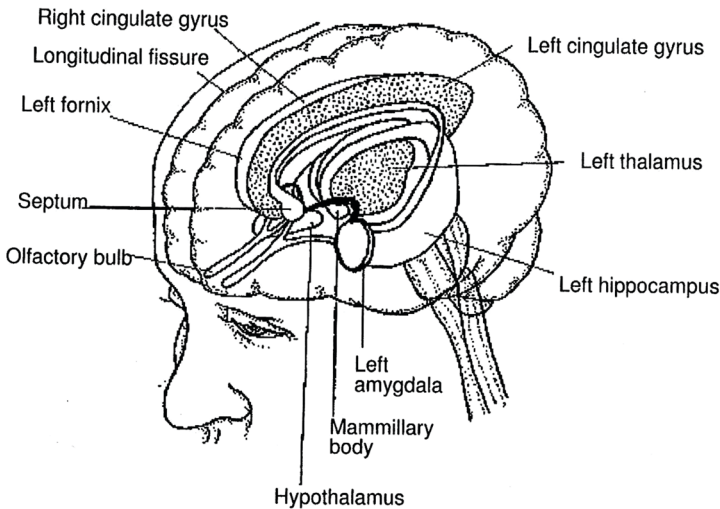
The thalamus is a central subcortical structure that receives all sensory inputs, except olfactory signals, with projections to the sensory area of the cortex (Figure 4.6). There are seven major anatomical nuclei that make up the thalamus, each with subdivisions. Thus, the thalamus is essentially a relay station where some integrative analysis does occur, but it primarily serves to pass information to higher brain centers. The thalamus also receives projections from the motor cortex and the sensory (e.g., pain) pathways from the spinal cord with the exception of olfactory tract (smell) neurons; all sensory pathways go through the thalamus. The structural appearance of the thalamus suggests its role as a sensory and motor relay station.

Hypothalamus

The hypothalamus is located just below the thalamus, hence its name (hypo = beneath, under; Figures 4.6 and 4.7). The hypothalamus also receives sensory input of many forms as well as input from all divisions of the brain. Because of its anatomic location, many fiber tracts from lower brain centers travel through the hypothalamus without making connections there. Electrical stimulation or destruction of different hypothalamic nuclei alters (among other functions) body weight, fluid intake, temperature regulation, and sexual and aggressive behavior (see Table 4.2). The hypothalamus communicates with the pituitary gland to regulate hormones as needed and to maintain homeostasis (keeping body functions in their normal limits).

Table 4.2 Biobehavioral Functions of the Hypothalamus

-
- Hunger
 - Thirst
 - Satiation
 - Temperature Regulation
 - Endocrine Regulation
 - Sexual Behavior
 - Pleasure
-

**Figure 4.7** Functional anatomy of subcortical limbic system structures

Limbic System

The limbic system (Figure 4.7) is involved in memory, emotion and drug effects. It consists of a number of interconnected brain structures, and includes the amygdala, hippocampus, hypothalamus, septum, nucleus accumbens, cingulate gyrus and parts of the cortex. Phineas Gage, whose story was told in Chapter 2, suffered severe damage to the limbic system and the dramatic emotional changes that followed. It has been suggested that addictions can be explained by emotional dysregulation. For example, emotions can range from euphoria to depression and pain. The brain regulates these to maintain homeostasis. Drugs may alter that balance by altering both brain reward and stress system responses.

Limbic system structures are anatomically interconnected, but an understanding of their functional inter-relationship with behavior slowly developing and complex. For example, the reinforcing effects of drugs involve the release of a neurochemical, dopamine, in the nucleus accumbens that can trigger changes in other basal ganglia circuits. Those circuits innervate distant brain structures resulting in behavioral changes. The basal ganglia is involved in voluntary motor control and some forms of learning including habits. The release of dopamine in the nucleus accumbens is also associated with the reward mechanisms involved in drug use.

Basal Ganglia

The basal ganglia are important in motor functioning and a key component of the extrapyramidal motor system (a major system coordinating movement). The basal ganglia consist of three major nuclei: the caudate nucleus, the putamen and the globus pallidus. These nuclei are rich in dopamine, serotonin, and acetylcholine and are involved in the initiation of movement.

Pituitary ("Master Gland")

The pituitary is an endocrine gland (Figure 4.5) and not part of the nervous system. It receives direct neural inputs as well as vascular (blood vessel) secretions from the hypothalamus. The pituitary releases numerous hormones into the circulation in response to direct nervous system inputs from the hypothalamus. Hormone release from glands (e.g., adrenal gland) may also be a result of the influence of hormone releasing "factors" from the hypothalamus. The pituitary also responds to circulating levels of hormones in the blood to regulate and maintain physiology.

Ventricles

Between the brain tissue and the skull is a protective envelope of cerebrospinal fluid (CSF). The CSF also travels through the brain in a communicating network of cavities called ventricles. Cerebrospinal fluid is the circulatory fluid of the nervous system, supplying the neurons and glia (cells that support

and nourish neurons) with the necessary nutrients and ions, and serving as a sink for the waste products of these cells.

The CSF, however, does not usually come in contact with neurons or bones directly. It is sheathed in tough layers of membranous tissue called meninges. The outermost layer is called the dura mater, the center layer is called the arachnoid membrane, and the innermost layer is called the pia mater. These are the membranes that are first visible when the cranial case (skull) is opened. They protect the nervous tissue from abrupt contact with the skull and confer some shape and substance to the otherwise jelly-like brain.

The CSF is slowly but constantly circulating between the arachnoid membrane and pia mater and through the ventricles that connect the brain and spinal cord. It is produced by the choroid plexus, an extension of the vasculature that protrudes into the lateral and third ventricles. Measurements of drugs, neurotransmitters, or their metabolites are sometimes made in the CSF as an indirect measure of what occurs to the chemistry and function of the brain.

Cranial Nerves

There are 12 cranial nerves that communicate information from the outside world to the brain. Receptors in the skin, nerves (of teeth), eye movements,

Table 4.3 Functional Aspects of the Cranial Nerves

Cranial Nerve	Name	Function
1	Olfactory	Smell
2	Optic	Vision
3	Ocularmotor	Eye movement
4	Trochlear	Eye muscles/movement
5	Trigeminal	Sensory – motor functions, sensations from scalp, jaw, face, teeth
6	Abducens	Eye muscles
7	Facial	Facial muscle movement
8	Vestibulocochlea	Balance, hearing
9	Glossopharyngeal	Taste, swallowing
10	Vagus	Heart muscles, sensations around ears and stomach
11	Accessory	Muscles in head, neck and shoulders
12	Hypoglossal	Tongue

tongue and elsewhere are sent information to the brain, allowing us to experience the world around us. Many of these nerves are affected by medical conditions, such as stroke, mechanical trauma or intoxication.

For example, intoxication may impair nerve signals to the hypoglossal nerve (slurred or thick speech), facial nerve (facial expressions), the vestibulocochlea nerve (balance) and other nerves.

Selected Bibliography

- Afiti, A. and Bergman, R. (2005). *Functional neuroanatomy*. McGraw-Hill Companies, Inc.
- Carpenter, M. (1976). *Human neuroanatomy*. Baltimore: Williams and Wilkins.
- Davidson, R. (2004). What does the prefrontal cortex “do” in affect: Perspectives on frontal EEG asymmetry research. *Biological Psychology*, 67: 219–233.
- Koob, G., (2015). The dark side of emotion: The addiction perspective. *European Journal of Pharmacology*, 753: 73–87.
- Pinel, J. (1990). *Biopsychology*, Needham Heights, MA: Allyn and Bacon.

Neurophysiology: How Do Psychoactive Drugs Act?

5

The discipline of neurophysiology has given us exciting new information about how brain cells (neurons) work, and how they interact to produce a “living computer” so complex that it may never be thoroughly understood. However, we have learned a tremendous amount about how neurons “talk” to one another through chemicals called “neurotransmitters”, and how these neurotransmitters act by affecting precise regions on nerve cells called “receptors.” As we shall see, most psychoactive drugs act on receptors, but a few of them act on nerve membranes or inside neurons to alter the transmission of electrochemical impulses. Whatever their mechanism, psychoactive drugs have a profound effect on (usually) large groups of brain cells to produce their pharmacological and behavioral effects.

The Bottom Line

We are now ready to enter the inner sanctum of neuropharmacology: neurophysiology – the study of brain cell function. This is where everything happens. Even without the aid of a microscope, the anatomical differences illustrated in Chapter 4 suggest differences in brain structures. Let’s take a closer look at the underlying cellular architecture and function of the brain.

Neurons, Glia, and Neurotransmission

As we learned in Chapter 4, the brain consists of two major types of cells: *neurons* and *glia*. Neurons are a specialized type of cell found only in the nervous systems of the body. Neurons transmit information about other parts of the body as well as the outside world via changes in an electrochemical process. It is the change in this *functional activity* (change in function but not structure) of neurons that produces all behavior, including intoxication and addiction to drugs.

Clusters of neurons form more specialized groups of brain structures called nuclei, while long axon extensions (see Figure 5.1) of neurons form fiber tracts that interconnect various nuclei allowing communication between specialized brain areas. For many years, it was believed neurons did almost everything and that glial cells were primarily involved in the structural support of neurons, had nutritive functions and provided the structure of the blood–brain barrier, described in Chapter 3. It is now known that glia, which outnumber neurons by 10:1 in some brain areas, may play key roles in neurodegenerative diseases and mental illness. Glia help guide neuron connections during brain development, communicate and modulate neuron activity, release neurochemicals and also have transporter mechanisms to move neurochemicals such as dopamine and serotonin back into cells after

2 Neurons and Parts

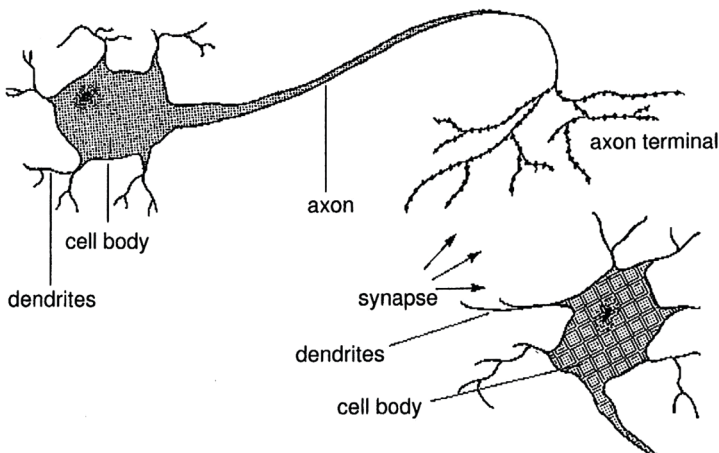


Figure 5.1 Spatial relationship between two neurons

they have been released. Glia are also involved in regulating synaptic strength which may be an important part of learning.

Each nucleus is composed of several hundred to several million neurons. To understand how drugs affect the brain, we must first understand how the basic unit of the brain, the neuron, is constructed and functions. Figure 5.1 shows the relationship of two typical neurons. You can see that the neurons are almost touching one another, but they are separated by a space. This space is called the *synapse*. As we shall see, it is across the synapse that neurons communicate chemical information to each other about the internal or external environment. In the brain a neuron will make synaptic contact with up to several thousand other neuronal inputs, but the human brain has nearly 100 billion neurons! Thus, our illustration is a very simplified representation of the complex arrangement of cells in the brain.

For a neuron to transmit its chemical message to another neuron, a series of events involving changes in electrical activity inside the cell must take place.

To begin with, neurons maintain an electrical charge called a *resting membrane potential*.

The resting membrane potential of all neurons is negative (-70 millivolts) in comparison to the charge outside the cell. The basis for this negative charge is the distribution of positively or negatively charged ions and other substances in and out of the neuron. The process of sending a chemical message from one cell to another is called *neurotransmission*. Neurotransmission starts with a change in the permeability of the cell membrane to various types ("species") of ions, such as sodium (Na^+), potassium (K^+) or chloride (Cl^-).

What Are Ions?

Ions are molecules that are the products of salts dissociated into different charged species. For example, if you add common table salt (sodium chloride or NaCl) to water, the positively charged sodium (Na^+) separates or dissociates from the negatively charged chloride (Cl^-). Two ionic species, Na^+ and Cl^- , each with opposite electrical charges, now exist in the water solution (Figure 5.2). As we shall see, the distribution of ions in and around brain cells is at the center of neurotransmission.

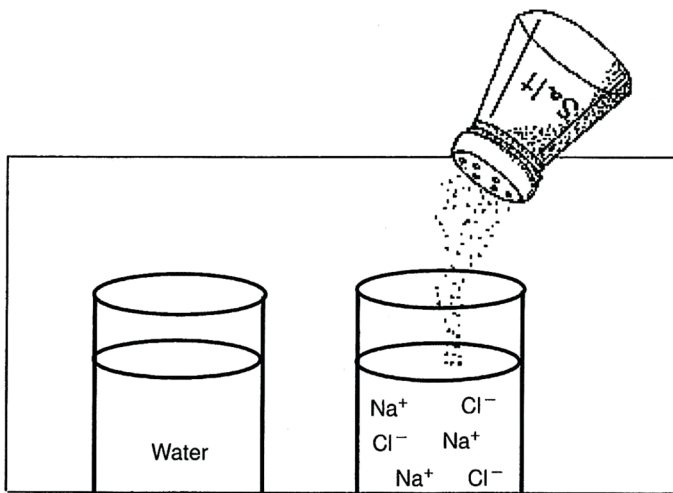


Figure 5.2 Dissociation of sodium chloride into two ionic species

Resting and Action Potentials Explained

In the brain, the membranes that make up neurons and specialized biological pumps do a good job of keeping certain ions out of the cell and preventing other ions from escaping from inside the cell. The distribution of variously charged ions and proteins between the inside and the outside of the neuron results in a resting electrical potential across the nerve membrane.

In many neurons, for example, the outer membrane covering of the cell keeps positively charged potassium (K^+) and negatively charged Cl^- ions and protein molecules inside the cell. Positively charged Na^+ ions and other ionic species are kept out of the cell. This results in a negative charge on the inside of the cell. The negative or positive charge is simply the net sum of the ionic balance at any point in time. Specialized biological membrane “pumps” help maintain this balance of a negative resting potential (Figure 5.3).

Ion-gated Neurotransmission

Certain physiological events, which we will discuss momentarily, alter the permeability of the membrane that maintains the resting potential. Because oppositely charged particles attract and like charges repel each other, when the permeability of the membrane changes and Na^+ rushes into the neuron,

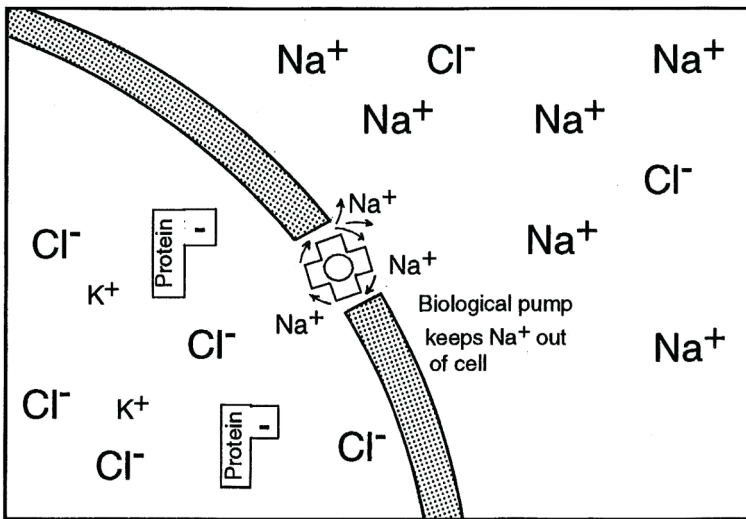


Figure 5.3 Distribution of sodium and potassium ions inside and outside a neuron

K^+ inside the neuron is repelled out. If enough ions are exchanged, the resting potential inside the cell becomes more and more positively charged, leading to a critical threshold that sets off an impulse, called an action potential. The action potential is a change in ion movement that travels down the length of the axon to the axon terminal, making the neuron more and more positively charged. When the action potential reaches the axon terminal of the neuron, it causes storage sacs called vesicles in the cell to move to the edge of the cell membrane and release chemicals stored in vesicles. The stored chemicals are called neurotransmitters or “first messengers” (discussed in detail below). This type of neurotransmission is called “ion-gated” because the process of neurotransmission is directly related to the changes in the charged ions. (While now a cliché, the movement of the action potential down an axon can be visualized as an old-time paper fireworks fuse filled with combustible chemicals burning as it travels after being lit by a match down to the firecracker, where it “explodes”, in this case in a release of neurotransmitters.)

Non-ion-gated Neurotransmission

Not all nerve-cell communication is dependent upon ion changes. Some neurons have protein-linked signaling in which specific molecules function as a “second

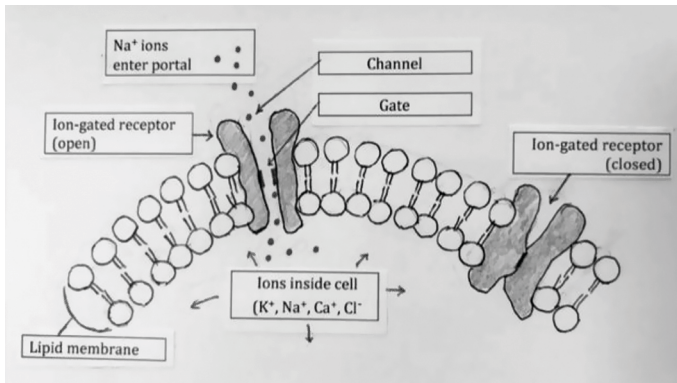


Figure 5.4 Diagram of ion-gated neurotransmission when the receptor gate is open

messenger” to initiate, amplify, and carry on signal transduction within the cell. In other words, the neurotransmitter may bind to a receptor to activate a “G-protein” that signals another change in the post-synaptic neuron.

The change is not related to ions, but to enzymes (e.g., adenylyl cyclase) inside the neuron. Adenylyl cyclase (see Figure 9.2) in turn transforms chemicals in the cell to “second messengers” that add phosphate ions to proteins in the cell. This phosphorylation of proteins decreases the interaction between neurotransmitters and their receptors. Some examples of second messengers are cyclic nucleotides such as cyclic adenosine monophosphate (cAMP), inositol-1,4,5-trisphosphate (IP₃) and diacylglycerol (DAG) and calcium ions. These and other second messengers may be linked to inhibitory or excitatory second messenger subtypes.

What Are Neurotransmitters?

Neurons, glia, and nuclei communicate information about changes in their internal or external environments through the release of a specific biochemical substance called a *neurotransmitter*. Neurotransmitters are manufactured and stored within the neuron and released as a consequence of the action potential. To date, more than sixty neurotransmitters have been identified. As we will see later, they can be inhibitory or excitatory in nature, meaning they increase or decrease the probability of an action potential in the neurons they contact. Some of the best-studied neurotransmitters, as well as some of the biobehavioral functions they relate to, are listed in Table 5.1.

Table 5.1 Neurotransmitters and Identified Functions

Neurotransmitter (–) inhibitory (+) excitatory	Identified function
Acetylcholine (+)	In both the brain and spinal cord and peripheral nervous system, acetylcholine is a key transmitter in the autonomic nervous system regulating cardiovascular and gastrointestinal motility, muscle contractions, memory, sleep, libido, motivation, motor systems, learning, nicotine dependence.
Aspartate (+)	The most abundant excitatory neurotransmitter found primarily in the spinal cord. Involved in alcohol intoxication, stimulates some but not all glutamate receptors.
Dopamine (±)	Key part of the brains reward system (pleasure, arousal and learning). Dopamine is involved in movement disorders (e.g., Parkinson's disease) memory, mood and motivation, drug craving and mental illnesses including schizophrenia, bipolar disorder and attention deficit hyperactivity.
Endocannabinoids (–)	Receptor for THC, the active ingredient in marijuana, mood, pain control.
Endorphins (–) (beta-endorphin, enkephalins, and dynorphins)	These chains of amino acids are made in the body and released in response to pain and the “feel good” runner's high. Endorphins are involved in learning, eating and affected by opioids.
Epinephrine (+)	Epinephrine (also called adrenaline) and the related catecholamine norepinephrine stimulate heart rate, respiration, blood pressure, blood sugar and blood flow and increase arousal as part of the “fight-or-flight” response to stress.
Gamma-aminobutyric acid (GABA) (–)	The most common inhibitory neurotransmitter in the brain. Regulates anxiety, mental concentration, sleep, seizures and depression and key transmitter in the actions of alcohol and benzodiazepines.
Glycine (–)	Found primarily in the spinal cord. Involved in hearing, pain transmission and metabolism
Glutamate (+)	Involved in the effects of alcohol and other intoxicating drug by stimulating NMDA receptors.

(continued)

Table 5.1 Cont.

Neurotransmitter (–) inhibitory (+) excitatory	Identified function
Histamine	Regulates sleep-waking cycles, feeding behavior and motivation.
Norepinephrine (+)	Also called noradrenaline, increases alertness, arousal, stress, attention, blood pressure and associated with mental illnesses. Decreased norepinephrine activity is associated with depression, whereas increased norepinephrine increases alertness and is associated with hyperactivity.
Phenylethylamine	Regulates monoamine transmission in the brain and also acts as a neurotransmitter. It is an amino acid precursor to tyrosine and dopamine. Also found in plants and foods and has stimulant properties.
Opioid peptides (–)	Pain regulation, learning, eating, “addiction”, relaxation, mood, pain control.
Orexin	Sleep-wake cycle, addiction, arousal, obesity, blood pressure, stimulates appetite.
Serotonin (–)	Inhibitory neurotransmitter that regulates mood, sleep patterns, anxiety, appetite, pain and associated with depression, seasonal affective anxiety disorders, depression, sleep, dreaming, and pain.
Substance P (–)	Pain perception, stress, mood disorders.

Where Do Neurotransmitters Come from?

Neurotransmitters are made inside neurons from biochemicals that are normally present in the brain and spinal cord. However, the source material needed in the manufacture of neurotransmitters come from outside the body. Some neurotransmitters are derived from amino acids, the building blocks of proteins. These neurotransmitters are referred to as biogenic amines. Their synthesis is dependent upon a good dietary supply of basic amino acids. If the diet is deficient, the brain will not be able to manufacture these neurotransmitters as needed. Table 5.2 lists the most common

Table 5.2 Dietary Precursors of Common Neurotransmitters

Neurotransmitter	Precursor	Foods
Acetylcholine	Choline	Eggs, hazelnuts, dairy products, organ meat (liver and kidneys), fish eggs (caviar), fish, soybeans, wheat germ.
Aspartate	Aspartic acid	Beef, chicken breast, nectarines, oysters, eggs, asparagus, avocado, peanuts, potatoes, whole grain, maize.
Dopamine	Phenylalanine	Haricot (i.e., kidney), beans, beets, soybeans, almonds, barley, eggs, meat, poultry, oats, grains, nuts (almonds, cashews, walnuts, peanuts).
Gamma-aminobutyric acid	Glutamate	Glutamates are found in most foods. Excess use is potentially harmful (see Glutamate, below).
Glutamate	Glutamic acid	White bread, flour, potatoes, processed meats cheese, Asian sauces (e.g., Mono Sodium Glutamate).
Norepinephrine	Tyrosine	Sesame seeds, cheese, soybeans, meat, poultry, fish, beets, nuts, peas, rice, dairy products.
Serotonin	Tryptophan	Chicken breast, turkey, lean pork, tofu, Sockeye salmon, milk, canned tuna, beets, spinach, coconuts, eggs.

neurotransmitters and foods that are rich in the essential amino acids that form the building blocks for these important chemicals.

The transport of amino acids into the brain for the manufacture of neurotransmitters is closely regulated. Not all substances can pass through the blood–brain barrier. The transport of amino acids is based upon a delicate balance of different proteins and amino acids in the blood, as well as the presence of carbohydrates. Were it not for the blood–brain barrier, every time you consumed or missed a meal your brain chemistry and resulting behavior would change dramatically! There is some research to suggest that dietary amino acids can provide some protection from stress-induced decreases in brain neurotransmitters like norepinephrine. While it is clear that a good diet is essential to good health in and outside the brain, dietary supplements to treat neurochemical disorders, such as Parkinson’s disease, schizophrenia, and drug addiction, have not been very successful.

Where Do Neurotransmitters Go?

Once released from the axon terminal of the neuron, neurotransmitters enter into the synapse between the axon terminal of one neuron and the cell body of another neuron. The neurotransmitter then comes in contact with receptors (binding sites) in the next neuron, located across the synapse from the axon terminal of the “first” neuron. Depending upon the type of receptor that it binds to, and the type of neurotransmitter, the neurotransmitter substance will then increase or decrease the probability of an action potential in the affected neuron. In some neurons, increases in ion flux that follow excitatory postsynaptic potentials (EPSPs) increase the probability of an action potential. Inhibitory postsynaptic potentials (IPSPs) that decrease ion flux in the postsynaptic neuron have the opposite effect – they decrease the probability of an action potential. This process takes place in thousands of neurons every second. After a fraction of a second, the neurotransmitter drifts back into the synapse. Multiply this by the number of neurons to appreciate how active the brain is.

Once back in the synapse a) the neurotransmitter may be broken down (“metabolized”) by enzymes, b) the neurotransmitter may contact other receptors, or c) neurotransporters may take it back into the neuron from which it came. This latter process was previously called “reuptake,” but the new name for the process is called “transport”. Inside the neuron, the neurotransmitter may be subject to enzymatic actions (i.e., breakdown) or may be repackaged into storage vesicles for future release. As we shall see, many psychoactive drugs affect the functional activity of neurotransmitters by altering metabolizing enzymes or the transport process. This series of events (“neurotransmission”) takes place in the brain many billions of times each second.

What Are Receptors?

Neurotransmitters interact with specialized protein receptors that are located on “sending neurons” (presynaptic side) as well as “receiving neurons” (postsynaptic side). The receptor itself is a special protein capable of recognizing a specific neurotransmitter molecule. To date, there are at least forty-six subtypes of receptors for neurotransmitters involved in psychoactive drug effects; some are located on the presynaptic neurons whereas others are on postsynaptic neurons. Some receptor subtypes have been identified

using specific binding chemicals, whereas other receptor subtypes have been identified using receptor-cloning techniques. In the latter case, these cloned receptors are awaiting discovery of compounds that will specifically interact with the receptors. When the receptor is occupied by a neurotransmitter, the receptor may initiate a series of biochemical changes that increase or decrease the permeability of the neuron, thereby increasing or decreasing the probability of an action potential. After the neurotransmitter makes contact with the receptor, it drifts off the receptor and back into the synapse, where it may remain active or be broken down by postsynaptic enzymes. One important enzyme in this process is monoamine oxidase (MAO). Monoamine oxidase inhibitors (MAOIs) block the effectiveness of MAO in metabolizing the neurotransmitter. This results in an increase in the bioavailability of the neurotransmitter. Some clinical antidepressants are MAOIs (Chapter 6) and some psychedelic drugs, such as harmaline contain MAOIs (see Chapter 14).

Neurotransmission, Drugs and Behavior

All psychoactive drugs produce their effects by altering the functional activity of neurotransmitters. It is this magnificent interplay in the functional activity of brain cells that enables us to perceive and respond to our external environment and to ponder a thought, remember a name, or become intoxicated by the scent of a perfume or by a drug.

There are four basic mechanisms by which a drug may change functional activity:

- Increase the release of a neurotransmitter
- Directly activate or blocking the neurotransmitter receptors
- Inhibit the reuptake (transport) of the transmitter into the neuron (this keeps it in the synapse where it is free to interact with receptors again)
- Inhibit enzymes in, or near, the neuron that would break down the neurotransmitter

As discussed in Chapter 3, psychoactive drugs that directly activate (agonists) or block (antagonists) receptors alter the functional activity of neurons at the receptor. Increases or decreases in the functional activity of various neurotransmitters can also occur directly or indirectly by changes in the manufacture, reuptake, or alteration of the enzymatic breakdown of neurotransmitters.

Some drugs can change the functional activity of the cell directly by altering the cellular membrane or the specialized cell structure around a neuron's receptors. Regardless of the mechanism of action, it is the change in the functional activity of neurons that causes all psychoactive drug effects.

Several identified neurotransmitters share structural similarities but most do not. In fact, they are quite different. Yet, there is a remarkable abundance of overlapping behaviors they regulate, which continues to demonstrate the remarkable complexity of the brain and behavior.

There Are No Coincidences

One of many remarkable revelations in neuropharmacology is the fact that we have receptors that react to sensory events (light, sound, touch, temperature) but also psychoactive drugs. As we shall learn, many psychoactive drugs not only have specific receptors so that they can affect the brain and behavior, but some drugs have molecular structures very similar to naturally present neurotransmitters (e.g., dopamine and norepinephrine). It is no coincidence that many psychotherapeutic medications exert their effects through the same neurochemical systems involved in drugs actions.

Selected Bibliography

- Brick, J. (1987). *Drugs and the brain*. New Brunswick, NJ: Rutgers University Center of Alcohol Studies.
- Diem, K. and Lentner, C. (1971). *Scientific tables*. Basle, Switzerland: Ciba-Geisn, Ltd., p. 516.
- Harris, G., Wimmer, M., and Aston-Jones, G. (2005). A role for lateral hypothalamic orexin neurons in reward seeking. *Nature*, 437(7058): 556–559.
- Jantti, M., Mandrika, I., and Kukkonen, J. (2014). Human orexin/hypocretin receptors form constitutive homo- and heteromeric complexes with each other and human CB1 cannabinoid receptors. *Biochemical and Biophysical Research Communications*, 445(2): 486–490.
- Kawamura, Y., Fukaya, M., Maejima, T., Yoshida, T., Miura, E., Watanabe, M., Ohno-Shosaku, T., and Kano, M. (2006). The CB1 cannabinoid receptor is the major cannabinoid receptor at excitatory presynaptic sites in the hippocampus and cerebellum. *The Journal of Neuroscience*, 26: 2991–3001.
- Livetrong.com (2023). Search of foods high in amino acids.
- Miller, G. (2005). The dark side of glia. *Science*, 308: 770–781.

- Tsuneki, H., Wada, T., and Sasaoka, T. (2010). Role of orexin in the regulation of glucose homeostasis. *Acta Physiologica*, 198(3): 335–348.
- Wilcox, R. E. and Gonzales, R. A. (1995). Introduction to neurotransmitters, receptors, signal transduction and second messengers. In: A. F. Schatzberg and C. B. Nemeroff (Eds.) *Textbook of psychopharmacology*. Washington, DC: American Psychiatric Press, Inc., pp. 3–30.
- WebMD.com (2023). Search of foods high in amino acids.

Antidepressants: Drugs That Lift Us Up

6

What Is Depression?

Mood disorders are characterized by different disturbances in affect or mood, and are divided into ten different types of depressive disorders. Mood disorders that include depression are estimated to affect six percent of the population in the US. A detailed description of the clinical features of these disorders can be found in DSM-V, but generally, all share one feature: debilitating changes in mood. In this chapter the term *clinical depression* will generally refer to major depressive disorders and other forms of depression that are not from physiological changes due to drug use problems, medications, or a medical condition. Different types of mood disorders are listed in Table 6.1. In this chapter, we will discuss the basic clinical symptomology of depression and psychotherapeutic drugs used to treat it.

Many people go through different periods in life and have experienced feelings of sadness, isolation, or helplessness that are “depressing”. Life is rarely without road bumps and it is normal to feel sad and unhappy when bad things happen. However, several features distinguish these feelings from clinical depression.

Clinical depression is more intense and longer lasting than “the blues”. In fact, depression is often so intense and lasts for so long that feelings of helplessness and indecisiveness interfere with normal day-to-day functioning for weeks, months, or longer. People cannot work at their jobs or get things done around the house. Depressed persons are often tearful, irritable, spend a lot of

Table 6.1 Types and Features of Mood Disorders*

Type	Characteristic features	
Major Depressive Disorder Lifetime prevalence: 10–25% women, 5–12% men	At least 2 weeks of depressed mood or loss of interest	Depressed mood most of the day, feels sad, may be tearful, loss of pleasure in all or most activities, weight changes, sleep disturbances, psychomotor agitation or retardation, loss of energy, feelings of worthlessness, guilt, helplessness, trouble concentrating, recurrent suicidal ideation
Bipolar Disorders Lifetime prevalence: 0.4–1.6%	One or more manic episodes (at least 1 week in duration) coupled with major depressive episodes	Inflated self-esteem, decreased need for sleep, very talkative, flight of ideas, easily distracted, increased goal directed activities, excessive involvement in pleasurable activities (unrestrained shopping, sexual indiscretions, foolish business investments)
Mood Disorders Due to Medical Condition occurs in 25–40% or higher, in patients with certain neurological conditions	Prominent and persistent disturbance – depressed mood and markedly decreased interest or pleasure in all or most activities; elevated, expansive or irritable mood	Symptoms related to Parkinson's, Huntington's, stroke, endocrine disorder, vitamin (e.g., B12), deficiency, viral infection, end-stage renal disease
Substance-Induced Mood Disorder	Due to prominent and persistent physiological effects of problem drug use, medication, or exposure to some toxin	Depressed, elevated, expansive, or irritable mood, markedly diminished pleasure or interest in most or all activities.

*Not inclusive of all relevant diagnostic criteria or types of depression/mood disorders. For general comparative information purposes only.

time sitting around, perhaps watching television or eating or lost in thought about their situation. Extreme changes in eating behavior such as loss of appetite and associated weight loss, or compulsive eating and weight gain, are often seen in depressed individuals. In some cases, eating is decreased because it just requires too much work. Depressed persons feel as though they have no energy or strength and nothing they do will make a difference.

Different antidepressant medications are often used to treat the preceding symptoms, or a range of diagnostic categories of depression. However, not all drugs are effective in treating the many different biobehavioral components of each type of depression. Why is this so? There are at least two reasons: individual differences between subjects may cause different responses to treatment, and drug treatments have or require different mechanisms. The neuropharmacology of the medication may simply lack the specificity of action needed to match the underlying biochemical causes of the depression. It is for these reasons that there is no one magic bullet, but a multitude of pharmacological treatment approaches (Table 6.2).

Traditional categories of depression included “endogenous” (no obvious precipitating cause) or “reactive” (reaction to an outside event such as the loss of a spouse or job). However, from a psychopharmacological perspective, the cause of the depression is not as important as the underlying neurophysiology. Most theories concerning the etiology (cause) of depression are derived from the relative effectiveness of major classes of antidepressant drugs used to treat depression (see Table 6.2). That these drugs are successful in treating depression, in many patients, and have relatively specific mechanisms of action strongly point to an underlying shared biochemical process in the expression of this behavioral disorder. Human behavior is complicated and no less so when the brain does not work properly, and illness follows. This explains, in part, why patients respond differently to pharmacotherapy. While the neurochemistry of depression is complex and not all antidepressant drugs alter the functional activity of one category of neurochemicals, one such

Table 6.2 Pharmacological Treatment Categories for Clinical Depression

-
- Monoamine Oxidase Inhibitors (MAOIs)
 - Selective Norepinephrine Reuptake Inhibitors (SNRIs)
 - Selective Serotonin Reuptake Inhibitors (SSRIs)
 - Tricyclic (TCAs) antidepressants
 - Tetracyclic (TeCAs) antidepressants
 - Neurokinin antagonists (endogenous receptor for Substance P)
 - NMDA antagonists (e.g., Ketamine)
-

group, monoamines and the “monoamine theory of depression” is where the story begins.

What Are Antidepressants?

Antidepressants are a broad category of medications that alter brain monoamines, a family of neurochemicals characterized by having a single biogenic amine group. The most common monoamines were discussed in Chapter 5. These are serotonin, norepinephrine and dopamine. Norepinephrine and dopamine are also in a separate and distinct category of neurochemicals called catecholamines. The difference between monoamines and catecholamines is directly related to their chemical configuration (Figure 6.1). Antidepressants exert their clinical effect by altering the

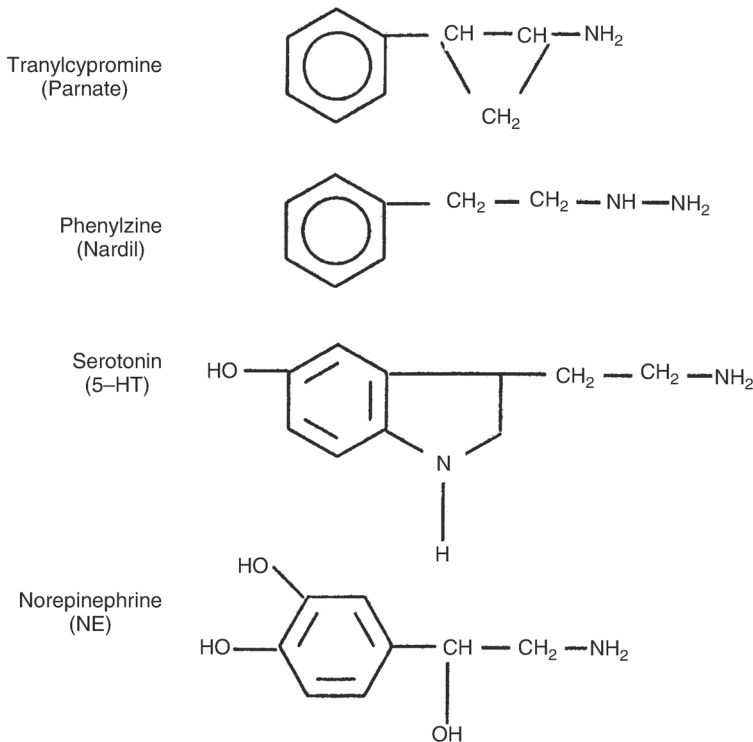


Figure 6.1 Structure of monoamines

functional activity (synthesis, reuptake, receptors, or metabolism) of one or more of these neurochemicals.

History of Antidepressant Medications

Long before pharmaceutical companies, scientists, psychologists, physicians or pharmacology came into existence, the stimulant properties of the Khat plant were known to people in and around the Arabian Peninsula for its euphoric effect and ability to reduce fatigue. The active ingredient in this plant (cathinone) may very well be the first form of antidepressant. Research in the pharmacology of this compound remained dormant until the 1930s.

Scientific breakthroughs are often serendipitous, as in the case of modern-day antidepressants. In the mid-1900s, tuberculosis, a lung disease caused by a bacterium was so widespread that special tuberculosis sanitariums were established but still overloaded with patients. The early therapy consisted of confining the individual, and treatment with very nonspecific drugs. In the 1950s, iproniazid was introduced. Iproniazid is an antibiotic that emptied the sanitariums except for those who were beyond recovery. The treatment with iproniazid had one interesting side effect. It caused some degree of elation on the wards. This improvement in mood was not totally unexpected because the patients were cured of a terrible disease. However, the mood improvement was persistent. A closer look at the medical history led to the realization that iproniazid was causing elation in patients who were previously “depressed” and long before they ever had tuberculosis. The term “psychic energizer” was coined and the first antidepressants were born. By 1952, iproniazid’s antidepressant effects had been found to be due to inhibition of the enzyme monoamine oxidase (MAO).

It was not surprising that the discovery of antidepressants (as well as antipsychotics discussed in Chapter 8) was serendipitous. Since MAO is an enzyme involved in the oxidation of norepinephrine, dopamine and serotonin, clinical effectiveness of drugs that altered monoamines suggested a biochemical cause of depression (and psychosis) that involved brain monoamines. By blocking the breakdown of monoamines, iproniazid increased the functional activity of these neurotransmitters, suggesting (more specifically) that depression was caused by a decrease in available monoamines, such as serotonin.

A short time later, one of the major and unifying biochemical theories of depression, the “norepinephrine theory of depression”, was developed. Schildkraut proposed that brain norepinephrine played an important part in

affective disorders and that depression was related to a decrease in the activity of endogenous norepinephrine, with mania being caused by an increase or overabundance of norepinephrine. Schildkraut's theory rested primarily on clinical changes in affect following pharmacological intervention. Drugs that increase the functional activity of noradrenergic neurons (those that release norepinephrine) are effective in alleviating clinical depression in many patients. Drugs that decrease the functional activity of these neurons lead to depression. Several categories of drugs that alter brain monoamines by increasing their functional activity are effective in treating depression. The neurochemistry of depression is far more complicated than increasing the activity of one brain chemical and we now know depression is a complex illness. Even so, the neuropharmacological changes in the brain affect behavior and, in many instances, treatment of depression includes a wide range of medications acting on one or many neurochemical systems. It is not possible to list every antidepressant available or every adverse effect of these medications but the major categories and most common side effects are discussed.

Categories of Antidepressants

Monoamine Oxidase Inhibitors

Monoamine oxidase is the enzyme that regulates intracellular catecholamines and thus catecholamine availability for neurotransmission. Although the postsynaptic effects of norepinephrine and dopamine are terminated primarily by their reuptake into the presynaptic terminal, the inhibition of MAO increases intracellular levels of catecholamines. MAO inhibitors (MAOIs) irreversibly and nonspecifically inactivate MAO-A and MAO-B, thereby increasing the functional activity of catecholamines. They are very successful in alleviating depression.

Some of more popular MAO inhibitors include phenelzine (Nardil), Tranylcypromine (Parnate), and generic isocarboxazid (Marplan) and selegiline (Eldepryl). MAOIs act by forming a stable complex with monoamine oxidase, thus preventing MAO from oxidizing intracellular catecholamines. Figure 6.1 shows the similarity between two popular MAOIs (Parnate and Nardil). It is the structural similarity between these drugs and the naturally occurring neurotransmitters (serotonin and norepinephrine) that enables the drug to bind to MAO instead of the neurotransmitter, thus inhibiting the action of MAO. Phenelzine (Nardil) and, to a greater extent, tranylcypromine

(Parnate), are effective antidepressants currently available in the United States. These drugs are “third-choice” antidepressants, however, because of their many side effects, such as postural hypotension (reduced blood pressure upon standing), liver damage and interaction with certain foods containing tyramine, which can lead to incidents of hypertension (high blood pressure). Iproniazid, the breakthrough MAOI linking depression with brain serotonin, is no longer used to treat depression and has been withdrawn from the market because it causes liver damage. However, all drugs have side effects that must be weighed against the therapeutic effectiveness of the medication.

Tricyclic Antidepressants

Drugs in this class increase the functional activity of norepinephrine, dopamine and serotonin by inhibiting the reuptake of these monoamines, thereby increasing their availability and activity in the synapse. Since these drugs all have a three-ring molecular structure, they are called tricyclic antidepressants. Imipramine (Tofranil) has been found to have an equal effect on the reuptake of serotonin and norepinephrine, whereas desipramine (Norpramin) is more specific to norepinephrine, and amitriptyline (Elavil) is more specific to serotonin. Although all of these are effective antidepressants, one may be more effective than the other in individual cases, based upon the clinical response of each depressed patient. It is also logical that lethargy and symptoms of retarded psychomotor behavior may be better treated with a tricyclic that primarily affects norepinephrine. A class of four-ring compounds, tetracyclics, was introduced in the 1970s for the treatment of depression. An example of a tetracyclic antidepressant is maprotiline (Ludiomil). Monoamine oxidase inhibitors and tricyclic medications are “first generation” antidepressants that have more adverse side effects than second and third generation medications. Some catecholamine reuptake inhibitors such as nomifensine have been taken off the U.S. market because of adverse treatment emergent side effects.

Lithium Salts

Lithium is sometimes prescribed as a treatment for people with symptoms of bipolar depression (episodes of mania and depression) or to treat people with unipolar depression. The exact mechanism of lithium’s action is somewhat unclear. Administered as a salt, the ion could substitute for several metals such

as Na^+ , K^+ , Mg^{++} or Ca^+ at various cellular sites. You will recall from Chapter 5 that changes in ionic flux alter neurotransmission. Lithium can increase the uptake of both tyrosine and tryptophan into synaptosomes, but its effect on catecholamine system activity is inconsistent. The nonspecificity of this drug is further indicated by its use in treating not only mania and depression but schizophrenia as well.

Stimulants

Since early pharmacological treatments for depression relied on simply increasing the functional activity of catecholamines, it was logical that stimulants (which have the same mechanism of action) might be effective. Cocaine and amphetamine or methylphenidate are useful in short-term treatment (i.e., a few days) of exogenous depression and to improve mood in nondepressed individuals. However, they do not provide satisfactory improvement in clinical depression that may last for weeks, months, or longer. Relatively short and certainly long-term use of such drugs has a high potential for misuse, addiction and withdrawal. In fact, subsequent abstinence from cocaine or amphetamine may induce depression (“substance-induced mood disorder”). For these reasons, cocaine and amphetamines are rarely recommended.

Serotonin and Norepinephrine Reuptake Inhibitors

Serotonin has consistently been a neurochemical of interest in the treatment of depression from the 1950s to the present. Today, some of the most widely used antidepressants are selective serotonin reuptake inhibitors (SSRIs) and selective norepinephrine reuptake inhibitors (SNRIs).

Rather than increasing the functional activity of brain serotonin by inhibiting MAO, SSRIs selectively inhibit serotonin reuptake. This is different from the nonselective mechanism by which tricyclics alter norepinephrine, dopamine and serotonin. SSRIs, when they were first introduced, rapidly became the mainstay of antidepressant pharmacotherapy. The most famous of these compounds is fluoxetine (Prozac). Others that have gained popularity include fluvoxamine (Luvox), duloxetine (Cymbalta), sertraline (Zoloft), paroxetine (Paxil), desvenlafaxine (Khedezia, Pristiq). All are slightly different in their clinical indications and side effects. In general,

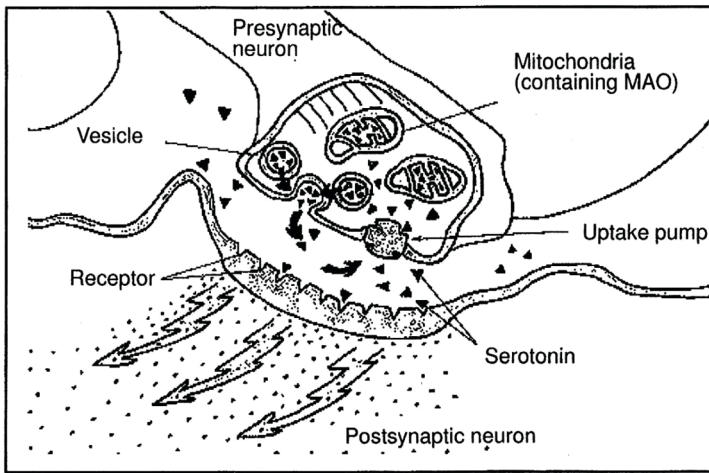


Figure 6.2 The mechanism of neurotransmission and serotonin reuptake inhibition is illustrated in Figure 6.2

their side effects are not as uncomfortable as those of other antidepressants although increased suicides have been noted with certain populations of depressed people treated with fluoxetine. Some antidepressants such as zimelidine (an SSRI) and nomifensine (a norepinephrine and dopamine reuptake inhibitor) have been taken off the U.S. market because of dangerous side effects (hemolytic anemia, hypersensitivity reactions and other adverse effects). Also, the use of brain serotonin altering medications has been linked to a potentially life-threatening “serotonin syndrome” in which elevated serotonin may cause agitation, confusion, sympathetic nervous system arousal including tachycardia, hypertension, mydriasis (dilated pupils), loss of coordination, and in severe cases, seizures, irregular heart rate and unconsciousness.

Neuropeptides

Although medications that alter monoamines continue to dominate in the treatment of depression, other neurochemical systems may also be important in treating psychiatric disorders. Modulation of the activity of neuropeptides such as substance P shows promise. Substance P is the most abundant neurokinin in the mammalian central nervous system and is involved in

regulating the response to stress and affective behavior. The distribution of Substance P throughout the brain also allows it to interact with two other neurochemicals involved in depression: norepinephrine and serotonin. Antagonism of Substance P has antidepressant effects that do not involve norepinephrine or serotonin, for example.

Faster Acting Antidepressants

Most antidepressants do not work immediately, requiring weeks or even months before any clinical change occurs. Moreover, a significant number of patients do not respond to antidepressants that increase the functional activity of norepinephrine or serotonin. It now is hypothesized that antidepressant effectiveness is related to a reorganization of neuron connections and communication and that such changes are made by increasing the turnover of synapses and other proteins involved in neural communication. Glutamate, the major excitatory neurotransmitter in the brain, is involved in the process and has rapid antidepressant effects. The receptor for brain glutamate is the N-methyl-d-aspartate (NMDA) receptor. Single doses of ketamine (a dissociative anesthetic), which blocks the NMDA receptor, reverses depression within hours of administration and has effects that last for at least one week. Although ketamine has adverse treatment emergent effects including psychotic-like symptoms and cognitive impairment, clinical trials with ketamine and other compounds that affect the glutamate system and NMDA receptors are in progress.

Other Medications

Drugs with mixed serotonin effects, such as trazodone (Desyrel) and nefazodone (Serzone) as well as mixed norepinephrine/dopamine uptake inhibition such as bupropion (Wellbutrin), have also been used to treat depression. Bupropion (trade name Zyban in this case) has also been found to be effective in smoking cessation. A final combined mechanism of action (serotonin/norepinephrine uptake inhibitor) is being tried in the form of venlafaxine (Effexor). This drug might be useful in treating patients who need a boost in synaptic norepinephrine and serotonin. See Table 6.3 for a list of antidepressants.

Table 6.3 Frequently Prescribed Antidepressants

Generic Name	Trade Name	Dose (mg)*	Elimination Half-Life (hr.)*
Tricyclics¹			
Imipramine	Tofranil	50–75	6–34
Amitriptyline	Elavil	50–75	9–46
Clomipramine	Anafranil	25–100	19–37
Doxepin	Sinequan	50–75	8–36
Desipramine	Norpramin	50–75	11–46
Nortriptyline	Pamelor	25–50	16–88
Protriptyline	Vivactil	10–20	54–198
Amoxapine	Asendin	50–150	8–30
Tetracyclics (mixed 5-HT/NE)			
Mianserin ³	Tolvon	30–90	10–27
Mirtazepine	Remeron	15–40	20–40
SSRIs²			
Citalopram	Celexa	20–40	35
Escitalopram	Lexapro	10–40	NA
Fluoxetine	Prozac	10–20	24–120
Fluvoxamine	Luvox	25–50	15–26
Paroxetine	Paxil	20	24–31
Sertraline	Zoloft	50–200	27
MAOIs¹			
Isocarboxizid	Marplan	10–40	NA
Phenelzine	Nardil	15	1.5–4
Tranylcypromine	Parnate	20	1.5–3
Mixed Serotonin Effects			
Trazodone	Desvrel	50–150	6–11
Mixed Reuptake Inhibitors			
Bupropion (NE/DA)	Wellbutrin, Zyban	200	10–21
Desvenlafaxine	Pristiq	50	11
Duloxetine (5HT/NE)	Cymbalta	20–30	12
Venlafaxine (5-HT/NE) ³	Effexor	75	5
NE Reuptake Inhibitors			
Atomoxetine	Strattera	40–80	5

*Doses used in clinical practice may be higher or lower than indicated, or titrated based on individual response. Values approximate.

¹First generation antidepressants. ² Second generation antidepressants.

³ Third generation antidepressant.

We would be remiss not to mention that while many patients are helped by pharmacotherapy and particularly the combination of antidepressants with some form of psychotherapy, not all people respond to antidepressants. Several studies suggest that antidepressants are most effective in cases of severe clinical depression. Some patients with milder forms of depression seem to respond to placebo treatment as well as antidepressants. Patients not yet treated with antidepressants should first explore nonpharmacological treatments, such as counseling. Prescribing and nonprescribing psychologists, physicians, and patients should keep this in mind as they assess treatment effectiveness.

Medical Consequences

All medications have some adverse effects and antidepressants are no exception. When pharmaceutical companies report adverse side effects on packaging, they do not always indicate the percentage of patients experienced those effects relative to placebo treated controls. It is therefore prudent to check the package insert for specific medications for additional information. The major unintended adverse effects of major categories of antidepressants are summarized in Table 6.4.

Antidepressants including zimelidine (an SSRI) and nomifensine have been taken off the U.S. market because of dangerous side effects.

Prenatal Effects

All medications have the potential to alter cell growth in the fetus during development, particularly during the early stages of pregnancy. Although early studies suggested that tricyclic antidepressant medications increased the risk for limb malformation, recent studies have not replicated this finding. Continued treatment with tricyclics (e.g., amitriptyline), SSRIs (e.g., fluoxetine) during pregnancy is considered an option but paroxetine (Paxil) is discouraged, particularly during the first trimester because of possible fetal heart defects. MAOIs are also discouraged during pregnancy.

At this time, there is sufficient data on the relationship between antidepressant medications and fetal development to suggest avoiding some medications. Women prescribed antidepressants who are pregnant or who plan on becoming pregnant should discuss this with their treating physician.

Table 6.4 Reported Side Effects of Antidepressants in Some Patients

Side Effects	SSRIs	SNRIs	TRYCYCLICS	MAOIs	5-HT RI/ AGONISTS
Headaches	X	X	X	-	-
Nausea	X	X	-	X	-
Trouble sleeping	X	X	-	-	-
Dizziness	X	X	X	X	X
Diarrhea	X	X	-	-	-
Decreased appetite	-	X	-	-	-
Weakness, fatigue	X	X	-	-	-
Anxiety	-	-	-	-	-
Stomach upset	X	X	X	X	-
Dry mouth	-	-	X	-	X
Sexual problems	X	X	X	-	-
Blurred vision	-	-	X	-	-
Constipation	-	-	X	-	X
Confusion or Memory problems	-	-	X	X	X
Trouble urinating	-	-	X	-	-
Weight gain	-	-	X	X	-
Hypotension	-	-	-	X	-

Tolerance and Dependence on Antidepressants

It is understandable that some people treated with antidepressants believe they are “addicting” because they improve mood and alleviate many other components of depression. Why would someone not want to continue using a medication that has a normalizing effect. However, this is very different from the drug craving associated with drugs like heroin. Similarly, some non-pharmacologists that apply the outmoded concept that define a drug as addicting if it creates tolerance, withdrawal or “psychological dependence”. It is now clear (see Chapter 16) that “psychological dependence (or addiction)” is a 1950s term that is no longer used. Furthermore, the mere presence of tolerance or withdrawal is insufficient to label someone as “addicted”. Antidepressants do produce tolerance, but it is mild compared to drug classes such as opioids, nicotine and even caffeine. Nevertheless, symptoms

Table 6.5 Signs and Symptoms of Antidepressant Withdrawal*

-
- irritability
 - anxiety
 - insomnia
 - headaches
 - dizziness
 - fatigue
 - nausea
 - symptoms of depression return
-

*Also known as “antidepressant discontinuation syndrome”

associated with withdrawal do occur (see Table 6.5) and patients prescribed antidepressants should not change their use or dose without supervision from the prescribing treatment specialist.

Characteristically it takes 7–14 days for antidepressants to exert their effect. For those looking for an immediate euphoria, this long period from use to effect is insufficiently reinforcing. Also, initial effects may produce some uncomfortable somatic and cognitive effects, which is another reason why antidepressants are not typically abused. In fact, there are no reports of people losing control over the use of their antidepressants. As testimony to their non-addictiveness, 12-step-centered treatment centers are now allowing patients on antidepressants to go through therapy for their drugs of choice, realizing that treatment is more effective in patients who are not depressed.

Many patients on antidepressants will go through withdrawal. Most of the symptoms of drug discontinuation are similar to adverse side effects (Table 6.5). When discontinuation is necessary or continued use not necessary, the dose should be tapered to reduce withdrawal severity – particularly if a patient has been on the medication for longer than six weeks.

Can antidepressants be misused? Absolutely, but this is not the same as “addiction”.

Finally, many common anti-depressants have been successfully used to treat chronic pain. Even though the pain relieving dose and application is different from use in treating depression, similar side effects, most notably dry mouth, headache, weight gain, thirst, constipation (amitriptyline, nortriptyline), drowsiness (venlafaxine), insomnia, vomiting, sweating, nausea (duloxetine), dizziness, sedation (Mirtazapine) and loss of libido (Fluoxetine) have been reported.

Forensic Considerations

Antidepressants are non-addicting and drug use problems are rare. They work on different brain areas than the addicting drugs such as alcohol, nicotine, cocaine, and heroin. They *can* be misused and overused (as in the case of ketamine). However, misuse of other antidepressants is very rare, and withdrawal symptoms are manageable with slow step-down dosing. Tolerance can occur in some people, but impaired control is also quite rare and generally, the presence of therapeutic amounts of antidepressant medications is of limited forensic interest, although the absence of prescribed use may be relevant to some behaviors. Many antidepressants exhibit post mortem redistribution meaning that the concentration measured in fatal cases may not represent the state of pharmacological activity prior to death. This is particularly critical in interpreting overdose or fatal cases. Pharmacokinetic and pharmacodynamic drug effects should always be evaluated on a case-by-case basis due to individual differences and circumstances and by a forensic toxicologist knowledgeable in the interpretation of ante- and post mortem drug findings.

Selected Bibliography

- Al-Motarreb, A., Baker, K. and Broadley, K. (2002). Khat: Pharmacological and medical aspects and its social use in Yemen. *Phytotherapy Research*, 16:5 403–413.
- Charney, D. S., Miller, H. L., Licinio, J., and Salomon, K. (1995). Treatment of depression. In: A. Schatzberg and C. Nemeroff (Eds.) *Textbook of psychopharmacology*. Washington, DC: American Psychiatric Press, pp. 575–602.
- Feldman, R. S. and Quenzer, L. F. (1984). *Fundamentals of neuropsychopharmacology*. Sunderland, MA: Sinauer Associates, pp. 369–398.
- Fournier, J. C., DeRubeis, R. J., Hollon, S. D., Dimidjian, S., Amsterdam, J. D., Shelton, R. C., and Fawcett, J. (2010). Antidepressant drug effects and depression severity: a patient-level meta-analysis. *JAMA*, 303(1): 47–53. doi:10.1001/jama.2009.1943
- Garblehner, G., Hansen, R. A., Thieda, P., DeVeaugh-Geiss, A. M., Gaynes, B. N., Krebs, E. E., Lux, L. J., Morgan, L. C., Shumate, J. A., Monroe, L. G., and Lohr, K. N. (2007). Comparative Effectiveness of Second-Generation Antidepressants in the Pharmacologic Treatment of Adult Depression. Comparative Effectiveness Review No. 7 (Prepared by RTI International-University of North Carolina Evidence-based Practice Center under Contract No. 290-02-0016.) Rockville, MD: Agency for Healthcare Research and Quality. Available at: www.effectivehealthcare.ahrq.gov/reports/final.cfm.

- Holden, C. (1991). Depression: The news isn't depressing. *Science*, 254: 1451–1452.
- Jingchun Sun and Zhongming Zhao (May 2010). Pathway-assisted investigation of atypical antipsychotic drugs and serotonin receptors in schizophrenia. *Biomedical Sciences and Engineering Conference (BSEC), 2010*, pp. 1–4, 25–26.
- Kramer, M., Cutler, N., Feighner, J., Shrivastava, R., Carman, J., Sramek, J., Reines, S., Liu, G., Snively, D., Wyatt-Knowles, E., Hale, J., Mills, S., MacCoss, M., Swain, C., Harrison, T., Hill, R., Hefti, F., Schonick, E., Cascieri, M., Chicchi, G., Sadowski, S., Williams, A., Hewson, L., Smith, D., Carlson, E., Hargreaves, R., and Rupniak, N. (1998). Distinct mechanisms for antidepressant activity by blockade of central substance P receptors. *Science*, 281: 1640–1645.
- Li, N., Lee, B., Liu, R., Banasr, M., Dwyer, J., Iwata, M., Li, X., Aghajanian, G., and Duman, R. (2010). mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists. *Science*, 329: 959–964.
- Potter, W., Manji, H. and Rudorfer, M. (1995). Tricyclics and tetracyclics. In: A. Schatzberg and C. Nemeroff (Eds.) *Textbook of psychopharmacology*. Washington, DC: American Psychiatric Press, pp. 141–160.
- Riediger, C., Schuster, T., Barlinn, K., Maier, S., Weitz, J., and Siepmann, T. (2017). Adverse effects of antidepressants for chronic pain: A systematic review and meta-analysis. *Frontiers in Neurology*, July 14(8): 307. doi: 10.3389/fneur.2017.00307. PMID: 28769859; PMCID: PMC5510574.
- Roth, B. and Meltz, H. (2000). The role of serotonin in schizophrenia. In: F. Bloom and D. Kupfer (Eds) *Psychopharmacology – The fourth generation of progress*. American College of Neuropsychopharmacology.
- Schildkraut, J. J. (1965). The catecholamine hypothesis of affective disorders: A review of supporting evidence. *American Journal of Psychiatry*, 122: 509–522.
- Stahl, S. M. and Palazidon, L. (1986). The pharmacology of depression. *Trends in Pharmacological Sciences*, 7: 349–354.

Anxiolytics: Drugs That Calm Us Down at a Cost

7

Anxiety is a common condition in humans who are under stress. In this chapter we will explore what happens when anxiety becomes uncontrollable and affects daily living. Antianxiety drugs (anxiolytics) have been designed to safely reduce anxiety while maintaining normal alertness. In this chapter we will explain how benzodiazepines, the prototype class of anxiolytic drugs, produce their effects when used in appropriate doses. When given to pharmacologically sensitive individuals, or in doses that are too high, or for too long a period of time, these drugs cause excessive drowsiness, dependence and other side effects. We will also review their misuse and addiction potential, and their therapeutic and nontherapeutic uses. Finally, anxiety is a common side effect of the use of drugs (particularly stimulants), and a common symptom of withdrawal from depressant drugs such as alcohol and nicotine.

What Is Anxiety?

From time to time, most people experience some form of anxiety. You may be worried about finances, lost your wallet or you are late for an important event. These everyday experiences may lead to feelings ranging from fear, to dread, to absolute terror depending upon the circumstances. These may be perfectly normal responses and usually brief. This is different from clinical anxiety. A major feature of clinical anxiety is that its victims do not know why they are anxious, even though their anxiety may be so severe as to be incapacitating.

Anxiety can evoke a number of autonomic nervous system responses. The responses are not under voluntary control and are part of the “fight or flight” reaction described in Chapter 1.

Charles Darwin (1809–1882), who is best known for his work on evolution, was also a very keen observer of how the perception of fear is expressed by the autonomic nervous system. Darwin’s observations made over a century ago are so accurate that they are well worth repeating in this chapter.

Fear is often preceded by astonishment ... the senses of sight and hearing being instantly aroused ... The eyes and mouth are widely opened, and the eyebrows raised ... [you stand] like a statue motionless and breathless, [crouching] instinctively to escape observation. The heart beats quickly and violently, so that it palpitates or knocks against the ribs ... [and] the skin instantly becomes pale ... due to the ... contraction of the small arteries of the skin. That the skin is much affected under the sense of great fear, we see in the marvelous and inexplicable manner in which perspiration immediately exudes from it. This exudation is all the more remarkable, as the surface is then cold, and hence the term a cold sweat ... the hairs also on the skin stand erect; and the superficial muscles shiver ... the heart, the breathing is hurried. The salivary glands act imperfectly; the mouth becomes dry, and is often opened and shut [and] ... there is a strong tendency to yawn. One of the best-marked symptoms is the trembling of all the muscles of the body; and this is often first seen in the lips ... the voice becomes husky or indistinct, or may altogether fail ... As fear increases into an agony of terror ... the heart beats wildly, or may fail to act and faintness ensue; there is a deathlike pallor; the breathing is labored; the wings of the nostrils are widely dilated; there is a gasping and convulsive motion of the lips, a tremor on the hollow cheek, a gulping and catching of the throat; the uncovered and protruding eyeballs are fixed on the object of terror; or they may roll restlessly from side to side ... The pupils are ... enormously dilated. All the muscles of the body may become rigid, or may be thrown into convulsive movements. The hands are alternatively clenched and opened, often with a twitching movement. The arms may be protruded, as if to avert some dreadful danger, or may be thrown wildly over the head ... In other cases there is a sudden and uncontrollable tendency to headlong flight ...

What Are Anxiety Disorders?

Anxiety disorders can include generalized anxiety disorder, panic disorder, agoraphobia (fear of venturing outside), social phobia, post-traumatic stress disorder and obsessive-compulsive disorder. Of these, the most studied are panic disorder, social phobia and post-traumatic stress disorders.

Anxiety produces a variety of subjective and physical symptoms (see Table 7.1). Visceral (inside organ) effects of anxiety originate in the hypothalamic-pituitary system and may include increased plasma nor-epinephrine, epinephrine (adrenaline), and the stress hormone cortisol. The motor symptoms, which include shakiness, tremor and muscular tension, a rise in the extrapyramidal motor system that controls voluntary movements.

Treatment of anxiety may focus on reducing physical symptoms as well as psychological triggers of anxiety. Treatment using psychoactive medication should almost always include psychotherapeutic treatment as well.

Anxiety is normal! Everyone experiences a certain amount of anxiety. Low-level anxiety is motivating and helpful. It is when anxiety is so intense that it is physically or emotionally incapacitating that it should be treated.

Table 7.1 Biobehavioral Symptoms of Anxiety

-
- hyperactivity (nervous movement)
 - fearfulness
 - withdrawal
 - palpitations
 - chest pain
 - sensations of choking/smothering
 - dizziness
 - feelings of unreality
 - paresthesia (tingling in hands or feet)
 - hot/cold flashes
 - sweating
 - trembling/shaking
 - fear of dying/going crazy or losing control
 - feelings of impending doom
 - dyspnea (difficulty in breathing)
-

Where Does Anxiety Begin?

Early studies of anxiety suggested that this disorder began outside the brain in the peripheral nervous system. It was believed that since the hormone adrenaline (epinephrine) stimulated the sympathetic nervous system (that part of the nervous system that responds to emergencies – the fight or flight response) and that anxiety was a sympathetic phenomenon as discussed in Chapter 4. It was theorized that if you could shut off the fight or flight response, you would reduce anxiety. It was quickly learned that although many of the sympathetic nervous system responses were triggered by adrenaline, the direct infusion of this hormone did not produce subjective feelings of anxiety. This observation and other work led to the suggestion that emotions such as fear and rage were initiated in the central nervous system. We now know that all such emotions emanate from the central nervous system. Therefore, changes in emotion must be produced by altering brain chemistry. Therapists are able to change brain chemistry through proper counseling techniques. Brain scan research indicate that cognitive behavioral therapy (CBT) does this very well, and so do antianxiety medications.

All antianxiety medications (i.e., anxiolytics) exert their effects on the central nervous system. However, peripheral-acting drugs, such as beta-blockers (e.g., propranolol) can decrease the unpleasant somatic effects associated with anxiety. Various neurotransmitter systems have been implicated in the causes of anxiety. Numerous pharmacological agents with different mechanisms of action have been employed to treat anxiety disorders. Although there is good evidence that norepinephrine and serotonin play some role in the production and treatment of anxiety disorders, the GABA system is clearly the most prominent player. More recently the treatment of anxiety through the use of antidepressant medications that affect the serotonin (5-HT) system suggests that 5-HT might also play a role in the causes of anxiety.

Pharmacological Treatment of Anxiety

Drugs used to treat anxiety are called anxiolytics, although other terms such as antianxiety drugs, minor tranquilizers (an old term), and sedatives have also been used. For the most part, these terms are interchangeable.

Drug Treatment of Anxiety

Over the centuries, various drugs have been used to treat anxiety. Alcohol is one of the oldest antianxiety drugs, and the interaction between alcohol and stress is well known. Under some circumstances and in some individuals, low doses of alcohol decrease the response to stress. However, alcohol's deleterious biomedical and psychosocial effects outweigh its overall usefulness as an anxiolytic. Phenobarbital, a sedative, was a popular antianxiety agent in the early 1900s. This barbiturate has a slow onset and long duration compared to shorter-acting barbiturates more commonly used as sleeping medications (e.g., secobarbital). Its use has declined because of a slow onset and too many side effects. However, the first true anxiolytic was chlordiazepoxide (Librium).

Development of Librium and Valium

The history and development of benzodiazepines is related more to luck than anything else. Leo Sternbach was a chemist working on developing dyes in Krakow, Poland in the 1930s. During his work, he synthesized a group of compounds known as heptodiazines. About 20 years later, Sternbach was working at Hoffman La Roche Pharmaceuticals in the United States and took a closer look at his earlier invention. As it turns out, Sternbach discovered that the drug he had synthesized 20 years earlier had sedative properties. The new drug was given an experimental name, RO 5-0690, and after considerable testing and refinement it became chlordiazepoxide (Librium). It is still popular.

In the years that followed, similar drugs were developed by Sternbach and eventually marketed. These included a type known as benzodiazepines, the best known of which is diazepam (Valium). At one time, benzodiazepines accounted for about half of all prescriptions written in the United States! Other benzodiazepines include: oxazepam (Serax), clorazepate (Tranxene), and lorazepam (Ativan). These drugs produce mild sedation (sleepiness), anxiolytic effects, muscle relaxation, and anticonvulsant effects. Different benzodiazepines have different therapeutic purposes.

Absorption, Distribution and Elimination

Heptodiazines and benzodiazepines are acids and are rapidly absorbed from the gastrointestinal tract. Peak blood levels can occur as quickly as thirty minutes to as long as three hours after oral administration, depending upon the specific anxiolytic. Some benzodiazepines may take up to eight hours to reach a maximum concentration in the blood, and blood levels can vary as much as twentyfold with the same dose in different people. Absorption following an oral dose is generally more rapid than by injection, since the drug tends to bind to proteins and does so more readily at an injection site than in the digestive tract. The absorption of benzodiazepines is increased by very low doses of alcohol and the combination of both drugs at high doses can be fatal.

Two Half-Lives

Benzodiazepines have a half-life of about two to ten hours, depending upon the particular drug and other factors. Much of the variation in bioavailability is because of distribution changes – the drug is easily taken up by fat tissue. The first phase of bioavailability is followed by a much slower elimination phase, with a half-life of 27 to 48 hours. Benzodiazepines have several metabolites (n-desmethyldiazepam, oxazepam) that are also psychoactive and extend the drug's effect for many more hours than the original parent compound. Therefore, the time it takes for the parent compound to reach maximum concentration (see above) may not reflect the time course for the achievement of maximum psychoactive effect. Since alcohol interferes with the metabolism of benzodiazepines and significantly increases their half-life (by about 50 percent), it is dangerous to use both of these together.

How Do Benzodiazepines Work?

Benzodiazepines alter the normal functioning of gamma amino butyric acid (GABA), one of the most abundant neurotransmitter systems in the brain. Let's examine how the GABA system normally works and how benzodiazepines affect it.

Normal GABA Functioning

Benzodiazepines interact with receptors on neurons that use the neurotransmitter gamma-aminobutyric acid (GABA) to change the functional activity of the cell. GABA acts as one of the brain's endogenous tranquilizing systems. When GABA receptors are occupied by GABA molecules, a Cl^- channel in the membrane of the cell opens, allowing ions to enter the cell and hyperpolarizing it, thus decreasing the probability of an action potential. Since this is an inhibitory action, GABA produces an IPSP (see Chapter 5). This neurochemical change, when produced in specific brain areas, is associated with relaxation and a decrease in anxiety.

In most people, behavioral states change rapidly according to environmental circumstances. The GABA system's role in such changes is governed by endogenous (made within the body) ligands, proteins synthesized in the body that bind to neurotransmitter receptors. These ligands inhibit GABA binding, thus reversing the relaxed, anxiety-free behavioral state. There are several such endogenous ligands, one of which is called GABA modulin. GABA modulin is a recognition receptor protein located in the neuronal membrane. When activated, GABA modulin works in concert with GABA to regulate Cl^- ion flow. The GABA modulin binds to the benzodiazepine recognition protein, inhibits GABA binding, and thus closes the Cl^- ion channel, decreasing IPSPs (see Figure 7.1).

Benzodiazepines Interfere with the GABA System

Benzodiazepine drugs have the opposite effect of endogenous benzodiazepine ligand; they increase the functional activity of the inhibitory amino acid neurotransmitter, GABA. By blocking the action of GABA modulin and/or other endogenous ligands, benzodiazepines increase the binding of GABA to its receptors and therefore increase postsynaptic IPSPs.

GABA must act as part of an anxiety-regulating network in the central nervous system. Normally, GABA binding is inhibited by one of several endogenous benzodiazepine ligands. This increases autonomic arousal and "good" anxiety. It keeps us vigilant, alert for changes in our environment, and so on. Under some conditions that are not fully understood, this state of arousal goes out of control, causing the clinical symptoms associated with an anxiety disorder. Benzodiazepines block GABA modulin (or perhaps some

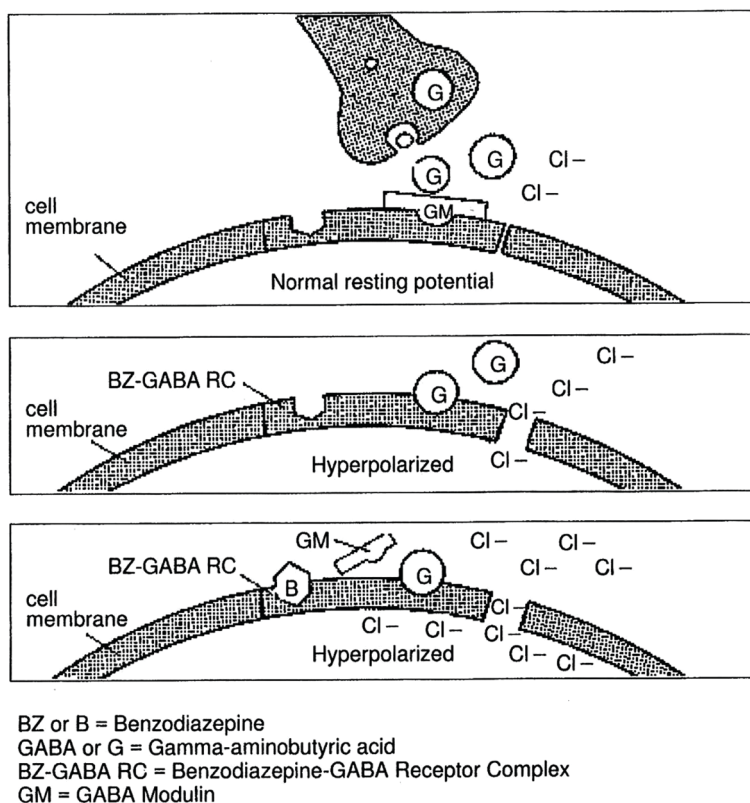


Figure 7.1 Benzodiazepine-GABA modulin receptor complex

other endogenous benzodiazepine ligand) and increase the postsynaptic binding of GABA. The increase in GABA receptor binding inhibits the brain's normal anxiety system.

Not all anxiolytics are benzodiazepines nor do all anxiolytics work through GABA. Some novel anxiolytics such as buspirone (BuSpar) are pharmacologically distinct from benzodiazepines and exerts their effects as a serotonin agonist.

Where Are Benzodiazepine Receptors?

Benzodiazepine receptors are distributed throughout the brain. The greatest concentrations are found in the frontal and occipital cortex, hypothalamus,

cerebellum, midbrain and hippocampus. Probable sites involved in benzodiazepine anxiolytic action are the septum, hippocampus, hypothalamus and other limbic system structures.

Biobehavioral Effects of Benzodiazepines

Anxiolytics

Benzodiazepines are effective anxiolytics. The primary use of benzodiazepines is to reduce anxiety without producing profound sedation. Lorazepam (Ativan) and alprazolam (Xanax) are popular anxiolytic benzodiazepines.

Motor Disorders

For the most part, the effects of benzodiazepines are limited to the central nervous system, even though many actions of this drug are seemingly outside the central nervous system. For example, a decrease in the muscular tension associated with anxiety is one prominent beneficial effect of benzodiazepines. In high doses, these drugs are used in the treatment of motor disorders such as Parkinson's disease, multiple sclerosis and brain injuries that produce increased muscular tone.

Seizures

Benzodiazepines also have anticonvulsant properties. For this reason, they are often prescribed during alcohol detoxification when patients are seizure-prone.

Insomnia

Benzodiazepines are also effective in treating insomnia. Flurazepam (Dalmane) is frequently used in the United States and nitrazepam (Mogadon) in Europe for this purpose. These benzodiazepines decrease the time it takes to fall asleep as well as the number of wakings during the night. Benzodiazepines decrease the amount of time spent in rapid eye movement (REM), stage III, and stage IV sleep, but this effect diminishes with use. When the drug is discontinued,

there is a rebound effect (REM, insomnia) that may last for one to two weeks. Increased REM is associated with bizarre dreaming, restlessness, and frequent awakenings during the night. These effects may be due to withdrawal (see Medical Consequences section at the end of this chapter).

Ataxia and Miscellaneous Effects

Benzodiazepines produce ataxia (lack of coordination) and drowsiness in 2 and 4 percent of the prescribed population, respectively. Occasionally, agitation, rage, aggression, depression, and sleep disorders also occur. Clinically administered for the treatment of anxiety, doses of more than 300 mg/day of Valium or 120 mg/day of Librium probably indicates another cause for anxiety, namely, overuse of the drug.

Mood and Driving

A number of studies have been performed to determine the effects of benzodiazepines on mood and psychophysical motor performance. These studies generally suggest that in driving studies, even low therapeutic doses produce some degree of impairment. For example, acute, low (1 mg) doses of Alprazolam significantly increase excursions out of lane, divided attention and memory errors. This effect is greater in immediate release (IR) than extended-release formulations. Higher doses of benzodiazepines have typical sedative hypnotic effects (e.g., confusion, impaired reaction time, ataxia, drowsiness) and any dose combined with other drugs that depress the central nervous system such as alcohol, opioids, barbiturates, etc., will have significant effects on a range of human behaviors, including complex tasks such as motor vehicle operation.

However, the generalization of these effects must be made cautiously for two reasons. First, most such studies used only single doses of the drug in a non-clinical population. In other words, the subjects were not diagnosed with anxiety disorders and who were treating with benzodiazepines for extended periods under medical supervision. When benzodiazepines are prescribed to treat anxiety disorders, the effects of these drugs on performance, such as operating a motor vehicle await further investigation. Those few studies that did use anxious subjects often reported improved performance, particularly when anxiety might be expected to interfere with test performance. This is discussed in more detail at the end of this chapter under Forensic Considerations.

Other Anxiolytic Medications

Meprobamate (Miltown, Equanil) was another early antianxiety agent. Meprobamate is a propyl alcohol derivative with pharmacological properties similar to benzodiazepines. It reduces anxiety without the sedation associated with barbiturates, although high doses do produce widespread central nervous system depression. At first, it was thought that meprobamate was less physically addicting than barbiturates. As it turned out, it was more addicting than originally believed, especially when taken over long periods of time. However, meprobamate is a relatively safe drug and overdoses are rare even with very high doses, except when it is taken in combination with other drugs. The combination of alcohol and meprobamate, for example, can be lethal. The use of meprobamate has declined in part because of the availability of newer, longer-acting benzodiazepines.

Buspirone (BuSpar) is a novel anxiolytic that is pharmacologically distinct from benzodiazepines. Buspirone increases brain serotonin activity (5-HT_{1a} agonist), has a low potential for misuse, produces little sedation or cognitive impairment, and its discontinuation is not associated with withdrawal symptoms.

Although antidepressants were developed to treat depression (see Chapter 6), they also help people with anxiety disorders. Many physicians prefer antidepressants, which do not produce chemical dependence (“addiction”), to the more dependence-producing and misused anxiolytics. Selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine (Prozac), sertraline (Zoloft), escitalopram (Lexapro), paroxetine (Paxil) and citalopram (Celexa) are commonly prescribed for panic disorder, obsessive-compulsive disorder (OCD), post-traumatic stress disorder (PTSD) and social phobia – all forms of anxiety. The serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine (Effexor) is commonly used to treat generalized anxiety disorder (GAD). The antidepressant bupropion (Wellbutrin) is also sometimes used. When treating anxiety disorders, antidepressants generally are started at low doses and increased over time.

Guidelines for the use of Medications to Treat Anxiety

1. Before prescribing, try to identify the life stressors that precipitate or aggravate anxiety that might be treated psychotherapeutically. In the case of a life event that cannot be altered by either therapy or drugs (e.g.,

Table 7.2 Dose Guidelines for Sedation**Benzodiazepine Derivatives**

- Xanax (alprazolam) 0.25–8 mg
- Librium (chlordiazepoxide) 10–25 mg
- Tranxene (clorazepate) 7.5–15 mg
- Valium (diazepam) 5–10 mg
- Klonopin (clonazepam) 0.5–1 mg (for panic disorders)

loss of a spouse, job), you must explain that the drug is only part of the treatment.

2. For chronic anxiety, the doses should be regulated. The patient should not use the drug “as needed” (see Table 7.2).
3. Use in combination with psychotherapy, not as a replacement for it.
4. Drug-free holidays should be encouraged. Usually a week or more is necessary to completely eliminate the drug and its active metabolites. In some cases, the use of a placebo such as a sugar tablet or a pseudoplacebo such as an antihistamine may be warranted.
5. Generally, older anxiolytics (e.g., meprobamate) are not used much anymore, because newer drugs have higher potency and require fewer doses per day for the same effect. Also, some physicians prefer antidepressant medications for the treatment of anxiety. All antianxiety drugs are useful, but different ones are used based upon patient response, physician preferences, and convenience of dosing.

Medical Consequences of Benzodiazepines

Addiction

Benzodiazepines have been used for more than 60 years. At first, only very high doses (100 to 600 mg/day) were believed to produced dependence. However, the widespread use of benzodiazepines over time have allowed a more careful look at the long-term adverse consequences of their use in treatment. More recent studies have revealed that high (135 mg/day) and low (20 mg/day) doses were capable of producing withdrawal (see Table 7.3). It is now clear that although these medications are effective anxiolytics, long-term use may cause serious and harmful dependence including serious withdrawal with both psychological and physical components. For

Table 7.3 Benzodiazepine Withdrawal Symptoms

-
- anxiety
 - amnesia and memory loss
 - sleep disturbances
 - sensitivity to bright lights and noise
 - increased auditory evoked potentials (experimental)
 - weight loss
 - unsteady gait
 - numbness or tingling (5 days to 2 weeks after abstinence)
 - delirium
-

example, psychological symptoms include anxiety, insomnia, depression, panic attacks, hallucinations, paranoid thinking, cognitive impairment (memory and concentration), delirium and even psychotic like behavior. Physical withdrawal symptoms include headache, seizures, tremor, tingling and numbness, a wide range of gastrointestinal problems and increased risk of suicide.

The withdrawal from benzodiazepines places certain populations at particular risk including: older persons, children and pregnant women. Older patients (over 65 years of age) are at high risk for fall down injuries, age-related cognitive decline (e.g., memory loss, confusion) as well as disturbances in sleep patterns. The use of benzodiazepines is known to cause psychomotor impairment, amnesia and memory loss. Pre-existing age-related behavioral and physiological changes will be exacerbated by use of benzodiazepines, placing older patients at increased risk. Withdrawal from benzodiazepines is similar to alcohol withdrawal and can be dangerous. Ironically, benzodiazepines are often administered to prevent seizures during alcohol withdrawal.

Children in intensive care units requiring sedation with midazolam have been reported to show signs of withdrawal (agitation, tremor, inconsolable crying and insomnia). Finally, pregnant women and their fetuses are subject to withdrawal.

Toxicity

Valium, one of the early benzodiazepines, has very low toxicity and does not activate liver microsomal enzymes. This means that Valium is unlikely to alter the metabolism of other drugs and thus their toxicity. Also, in comparison to other anxiolytics, the potential for misuse, although present, is relatively low.

Doses as high as 2250 mg of Librium have been reported without the deep coma and respiratory depression effects seen with other sedative-hypnotics. However, alprazolam deaths from suicide involved blood concentrations roughly 25 times more than therapeutic doses. The wide range of blood concentrations detected in driving under influence arrests also indicate large differences in the response to this drug. However, the combination of anxiolytics with alcohol can be fatal, particularly at high doses.

Benzodiazepines and the Fetus

Like most psychoactive drugs, benzodiazepines cross the placental barrier easily and also appear in the milk of nursing mothers. Although there are little data to suggest that benzodiazepine use during pregnancy produces birth defects, infants born of mothers using benzodiazepines at therapeutic doses show withdrawal symptoms such as tremors, irritability and hyperactivity at birth. These are similar to opiate withdrawal. Pregnant women are thus advised not to use benzodiazepines. Women prescribed anxiolytic medications who are pregnant or who plan on becoming pregnant should notify their treating physician.

Forensic Considerations

Unless combined with other drugs, including alcohol, benzodiazepines are rarely found in fatal overdose cases, because of their relative safety even in high doses. Nevertheless, benzodiazepine intoxication is a factor in many driving while intoxicated arrests and is one of the most common drugs present with alcohol or opiates. Even in therapeutic doses, driving is impaired. Although there is still insufficient data on the effects of long-term therapeutic doses of benzodiazepines on driving ability in patients with anxiety disorders, initial doses or subsequent higher doses of benzodiazepines will nevertheless produce typical sedative hypnotic effects (e.g., confusion, impaired reaction time, ataxia, drowsiness).

As noted, relatively low therapeutic doses of alprazolam produce impairment in driving related skills both in laboratory tests as well as actual motor vehicle operation. For example, Alprazolam (1 mg) significantly increases excursions out of lane, divided attention and memory errors and has been compared with BACs of 150 mg/dL (.15 percent). This effect is greater in

immediate release (IR) than extended release (XR) but all formulations produce dose proportional psychomotor impairment directly (as observed in driving studies) or indirectly (as observed in laboratory testing). Also, the combination of benzodiazepines with other drugs that depress the central nervous system such as opiate agonists (e.g., buprenorphine) or alcohol, will probably interact to deleteriously affect a range of human behaviors, including complex tasks such as motor vehicle operation further increasing the risk for an accident.

Finally, many benzodiazepines exhibit post mortem redistribution meaning that the concentration measured in fatal cases may not represent the state of intoxication prior to death. This is particularly critical in interpreting overdose or fatal cases. Pharmacokinetic and pharmacodynamic drug effects should always be evaluated on a case-by-case basis due to individual differences and circumstances and by a forensic toxicologist knowledgeable in the interpretation of ante- and post mortem drug findings.

Selected Bibliography

- Ballenger, J. (1995). Benzodiazepines. In: A. Schatzberg and C. Nemeroff (Eds.) *Textbook of psychopharmacology*. Washington, DC: American Psychiatric Press, pp. 215–230.
- Baselt, R., (2014). *Disposition of toxic drugs in man*, 10th Edition, Biomedical Publications.
- Brick, J. and Pohorecky, L. A. (Eds.) (1983). *Stress and alcohol use*. New York: Elsevier Biomedical, pp. 389–402.
- Darwin, C. (1872). *The expression of emotions in man and animals*. London: John Murry.
- Edinoff, A., Nix, C. and Hollier, J. (2021). Benzodiazepines: Use, dangers and clinical considerations. *Neurology International*, 13(4): 594–607.
- Leufkens, T., Vermeeren, A., Smink, B., Van Ruitenbeek, P. and Ramaekers, J. (2007). Cognitive, psychomotor and actual driving performance in healthy volunteers after immediate and extended release formulations of alprazolam 1 mg. *Psychopharmacology* (Berl), 181(4): 951–959.
- Logan, B. K. and Kay, G. (2011). Drugged Driving Expert Panel report: A consensus protocol for assessing the potential of drugs to impair driving. (DOT HS 811 438). Washington, DC: National Highway Traffic Safety Administration.
- Verster, J., Volkerts, E. and Verbaten, M. (2002). Effects of alprazolam on driving ability, memory functioning and psychomotor performance: A randomized, placebo-controlled study. *Neuropsychopharmacology*, 27(2): 260–269.

Antipsychotics: Drugs That Make Us Sane

8

Serious mental illness is highly correlated with drug use disorders. Among adults with psychiatric disorders, about 23 percent are problem users or dependent on alcohol or other drugs. Major psychoses such as manic depression (bipolar illness) or schizophrenia are brain diseases that are not the fault of the victim. While many factors are involved in these psychopathologies, the primary causes appear to be disruptions of brain chemistry in parts of the brain dealing with sensory perception and mood. Before the advent of the Golden Age of Pharmacology of the 1950s, the best we could do for psychotic patients was to give them high doses of alcohol, bromides, or morphine. In this chapter, we will discuss current antipsychotic medications (neuroleptics) that involve more sophisticated, more specific, and less toxic compounds to normalize mood and reduce delusions and hallucinations. Nevertheless, psychoses are still not managed as effectively as we would like, and this area remains a frontier for the sciences of neurobiology and neuropharmacology, particularly in patients with comorbid psychiatric and drug use issues. Let's take a closer look at the psychopharmacology of psychosis.

History of Antipsychotic Medications

Antecedents of pharmacological treatment of schizophrenia were crude, to say the least. Cold-water dunking, bleeding patients with leeches or burning people at the stake were common. Less than a hundred years ago, straitjackets and other restraints were considered acceptable treatments. Insulin-induced

coma, electroconvulsive shock and psychosurgery (e.g., lobotomies) were also used routinely to treat this disease. All that changed in the 1950s with the advent of antipsychotics medications, Reserpine and Thorazine (and iproniazid, an antidepressant discussed in Chapter 6). Thus began the Golden Age of Pharmacology.

The first of these antipsychotic medications was reserpine (Serpasil). Reserpine destroys the vesicles that store monoamine neurotransmitters. In short and in technical terms, the first antipsychotic medication was a monoaminergic antagonist. It calmed the schizophrenic, restoring behavior to a relatively normal degree without causing significant sedation. Reserpine's use was short-lived, however, because a second, more effective drug, chlorpromazine, was introduced at about the same time.

Chlorpromazine (Thorazine) was developed in France as part of a study of hibernation where it was found to lower body temperature and to exert a quieting effect on subjects. However, in searching for a drug that would reduce preoperative anxiety, scientists found that chlorpromazine went even further and made normal patients indifferent about the upcoming operation. Eventually, the drug was tested in schizophrenics and produced similar results (it causes a selective reduction in abnormal behavior with only mild sedation). At doses that would not alter the behavior of a normal individual, chlorpromazine quieted the psychotic episodes of schizophrenics. Furthermore, it had fewer side effects than reserpine and a very high therapeutic index. Chlorpromazine replaced reserpine as the drug of choice in the treatment of schizophrenia. Soon thereafter, it was discovered that chlorpromazine has a major effect on dopamine in the brain (Figure 8.1), which give scientists an important clue as to the cause of schizophrenia.

Psychiatric hospital records between 1900 and 1955 reveal that the number of beds occupied by psychiatric patients had increased steadily. Immediately following the introduction of reserpine and chlorpromazine, the number of hospital beds occupied by psychiatric patients declined dramatically. These data suggested quite convincingly that schizophrenia is a biological disorder best treated by a neuropharmacological approach. Today, using a variety of psychotherapeutic medications and techniques, approximately 50 percent of schizophrenics and patients with other psychoses show clinical improvement, compared to about 25 percent who respond positively to placebo. This therapeutic area has been the target of several controversies, from questions regarding whether patients are being chemically controlled, to the importance of maintenance therapy, to the accuracy of advertising of these medications by the pharmaceutical industry. Nevertheless, these drugs are

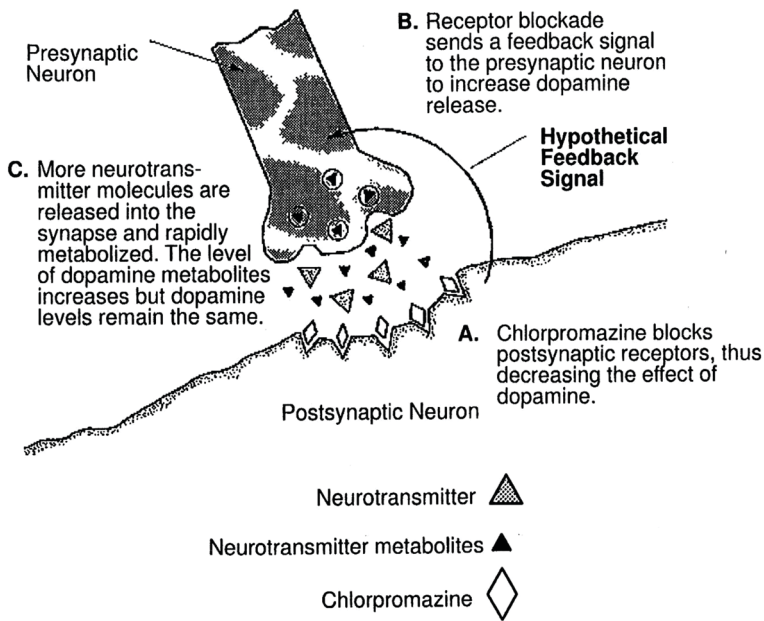


Figure 8.1 The effects of chlorpromazine on dopamine

extremely valuable for certain patients who would otherwise continue their terrible symptoms without any help, and the medications represent a major advance in the therapy of previously untreated patients.

What Is Psychosis?

Of all the behaviors in the human repertoire, the various forms of psychosis such as schizophrenia, schizoaffective disorder, affective disorders with psychosis, etc., are probably the most bizarre, the most interesting and the most baffling. Psychoses are complex, sometimes culturally confounded disorders whose diagnoses are based upon a constellation of symptoms and signs, rather than a single behavior and occurs in about 1 percent of the population. If you have not personally worked with schizophrenics (for example), it may be difficult to fully appreciate the treatment advances provided by psychotherapeutic medications.

Schizophrenia is prototypical and the most complex of all psychoses. Broadly defined, schizophrenia may be acute or chronic. Acute schizophrenia

has a sudden onset with full-blown symptoms but a good prognosis. Chronic schizophrenia has a gradual onset, the symptoms become progressively worse, and the prognosis is poor. Generally, schizophrenics have disturbances concerning reality testing and concept formation, psychomotor poverty and disorganization. In patients with comorbid psychiatric and drug use disorders the diagnosis, treatment and outcome are complicated because of the difficulty in diagnosing and treating two different disorders at the same time. Such dual-disorders have multiple negative consequences including work, home, legal, psychological and medical problems.

Signs and Symptoms of Schizophrenia

Thinking and Speech Disturbances

Schizophrenics have paralogical thinking (primitive thinking), distortions of memory, perplexity and confusion, often with feelings of unusual power. They may speak in rhymes using made-up words (neologisms) or use monotonous repetitive words or sentences. Some schizophrenics may be mute, whereas others may talk constantly. Schizophrenics have delusions of influence, grandeur, persecution or reference.

Catatonic Motor Behavior

Some schizophrenics have motor disturbances (psychomotor poverty). These patients may remain in rigid, unusual positions for extended periods of time, displaying what is described as waxy flexibility. Often, in their delusion, they may believe that the balance of the world as they know it is dependent upon their posture.

Schizophrenic Hallucinations

Auditory as well as other hallucinations may be present. Usually, patients hear voices of real or imaginary people who talk to, threaten, accuse, curse, or criticize them. "Visions" may be of angels and devils. Hallucinations of smell, taste, and touch often occur. Some patients may experience peculiar sensations in their genitals caused by some "other".

Disturbances of Affect and Emotion

Some forms of schizophrenia include flatness of emotion or inappropriate emotion. Acute schizophrenics frequently manifest anxieties and fears resulting in excitement and panic, or they may show depression, apathy or lethargy. Emotional behaviors are often combined with confused thinking, perplexity, fearful dream states and dissociative phenomena (e.g., disturbances in identity, memory or consciousness).

Disturbances of Social Behavior

These disturbances are characterized by social deterioration and sometimes complete regression from social contact. In some cases, even attention to bodily functions deteriorates (e.g., eating, urinating, defecating, personal appearance and cleanliness). Unpredictable giggling, silly behavioral mannerisms, aggression, and loss of interest in intellectual and social pursuits may also be symptoms of schizophrenia.

Some of these signs and symptoms may sound similar to descriptions of people under the influence of some illicit drugs (e.g., psychomotor impairment, hallucinations, depression) or in the end stages of addiction. There are some remarkable similarities in the neuropharmacology of intoxication and psychotic behavior, but do not jump to the conclusion that intoxication is the cause of psychosis! In fact, it is important in diagnosing schizophrenia to rule out medical or drug related causes of the behavior. Let's begin with the basic pharmacology of antipsychotics then take a closer look at what the treatment of schizophrenia has taught us about the neurochemical cause of this disease.

Pharmacology of Antipsychotics

Absorption, Distribution and Metabolism of Antipsychotics

Most antipsychotics are administered by mouth (oral) although in cases of severe episodes where patient safety may require very rapid delivery, injections are sometimes used. As with most therapeutic drugs, maintaining steady state blood concentrations is important for treatment. The majority of medications are administered daily but the extended half-life of some antipsychotics is

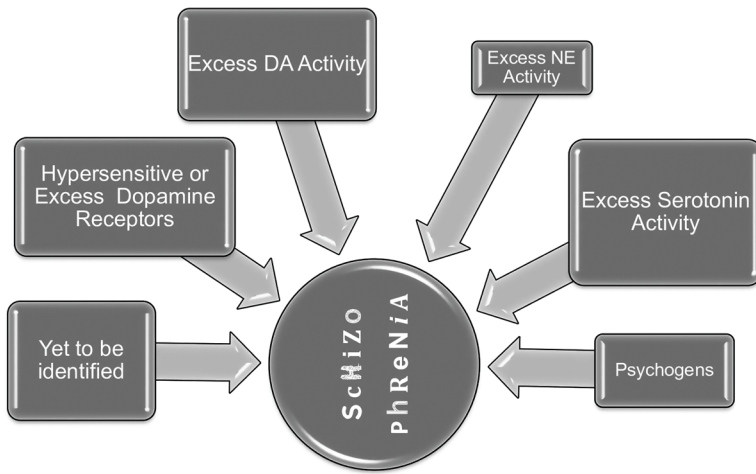


Figure 8.2 Multifactor model of schizophrenia

such that single weekly doses may be administered. The metabolism of these medications is often complex, resulting in active metabolites that may continue to alter behavior for many days after initial use.

As with other psychoactive drugs, antipsychotics exert their effect on behavior by altering the functional activity of brain neurochemicals, particularly dopamine and serotonin. The effectiveness of early antipsychotic medications quickly and clearly pointed to the role of brain dopamine in this mental illness. The symptoms of schizophrenia result from a biological imbalance within the brain's dopamine system. Although we still do not know precisely what aspect of the dopaminergic system is overactive, we now have some exciting insights (see Figure 8.2). There is also convincing evidence that brain serotonin or the interaction between serotonin and dopamine is involved in psychosis as well.

There are two broad categories of antipsychotic medications: Typical and Atypical and two broad schools of thought regarding the etiology of treatment of psychoses: The Dopamine Model and the Serotonin Model.

Phenothiazines: The Typical Antipsychotics

Chlorpromazine is the prototype for a number of phenothiazine antipsychotic drugs (see Table 8.1). Many of these “typical antipsychotics” are

Table 8.1 Major Categories and Pharmacology of Antipsychotics

Drug	Trade Name	Dose* (mg)	Half-Life** (hrs)
<u>Typical Antipsychotics</u>			
(Primarily dopamine antagonists)			
Butyrophenones			
Haloperidol	Haldol	5–100***	12–24
Diphenylbutylpiperidine			
Pimozide	Orap	2–6	20–53
Phenothiazines			
Chlorpromazine	Thorazine	100–800	16–30
Fluphenazine	Prolixin	2–20***	13–58
Perphenazine	Trilafon	8–64***	8–12
Thioridazine	Mellaril	200–800	21–25
Trifluoperazine	Stelazine	15–40	4–22 multiphasic
Thioxanthenes			
Chlorprothixene	Taractan	50–400	8–12
Thiothixene	Navane	6–60	10–30
<u>Atypical Antipsychotics</u>			
(Antagonists of multiple subsets of serotonin, norepinephrine and dopamine receptors)			
Benzisoxazole			
Aripiprazole	Abilify	10–30	75
Olanzapine	Zyprexa	10–20	21–54
Quetiapine	Seroquel	150–600	3–9
Risperidone	Risperdal	2–16	3–20 (incl. metab)
Ziprasidone	Geodon	60–80	4–8
Dibenzoxazepines			
Clozapine	Clozaril	100–900	6–17
Loxapine	Loxitane	20–60	3–4

*Initial doses are often lower (or higher) based on severity of illness, age, and individual responses. Doses often titrated up or down.

**May vary greatly based upon dose, route of administration, chronicity, multiphase elimination, inpatient or outpatient conditions or other factors.

***Larger doses or longer acting formulations sometimes administered once per week.

still in use today. Phenothiazines and most related antipsychotic medications share similar mechanisms of actions. They are dopamine antagonists.

Schizophrenia, Excess Brain Dopamine and the Basis of Therapeutics

The most convincing evidence for the dopamine theory of schizophrenia is the consistent observation that drugs that antagonize the dopamine system are effective in reducing schizophrenic behavior. Similarly, chronic high doses of drugs such as amphetamine or cocaine that activate the dopaminergic system produce schizophrenic-like behavior in the otherwise normal individual. If schizophrenic-like behavior is a disorder reflecting an overactive dopamine system, what is the physiological basis for this overactivity? Although there are many interesting approaches to answer this question, we will discuss only a few.

Too Much Dopamine?

The first possibility is that the brain of the schizophrenic has too much dopamine. This is certainly the simplest explanation. In spite of numerous attempts to measure this, however, there remains no convincing evidence that even a subpopulation of schizophrenics have too much dopamine in their brains. This is too simple an explanation.

Excess Dopamine Receptors?

The next possibility is that there are too many dopamine receptors in the brain of the schizophrenic. Many of the earlier studies of this hypothesis were confounded by the use of antipsychotic medications, since these drugs will increase the number of dopamine receptors. However, dopamine receptor binding studies using postmortem brain tissue from schizophrenics versus a matched set of controls show that schizophrenics do, in fact, have more dopamine receptor sites than non-schizophrenics. The inference is that a little dopamine goes a lot further in the schizophrenic because of the abundance of receptors.

Role of Monoamine Oxidase

It appears that schizophrenics have much lower levels of activity of brain neuronal monoamine oxidase, an enzyme that metabolizes dopamine. Therefore, in patients with low enzyme levels, dopamine would be present for longer periods of time in the brains of the schizophrenic. Blood platelets also contain the enzyme monoamine oxidase. Since schizophrenics have low platelet MAO, this may be a useful biological marker for this disease.

Endogenous Psychogens (Naturally Present Schizophrenia-Producing Chemicals)

Some scientists have theorized that the brains of schizophrenics are producing an unusual amount of phenylethylamine. Phenylethylamine is a dopaminergic agonist, an amphetamine-like stimulant normally found in low concentrations in brain tissue. Some investigators have observed unusually high concentrations of phenylethylamine in the brains of schizophrenics. Interest in endogenous psychogens, allergens, and similar chemicals has waned over the years because research in this area has not been very productive.

Abnormal Norepinephrine Metabolism May Alter Brain Dopamine

Schizophrenia may also be a disease caused by the destruction of brain norepinephrine-containing neurons resulting in an abnormal metabolism of dopamine in schizophrenics. Why? Because normally dopamine is metabolized to norepinephrine by the enzyme dopamine-beta-hydroxylase (DBH). There is some evidence that schizophrenics have lowered DBH activity, which leads to an increased accumulation of dopamine.

Where do Dopamine Antagonists Work?

Until recently, the dopamine hypothesis of schizophrenia was by far the best-accepted explanation of this disease, and is based on the fact that drugs that block dopamine receptors effectively treat the symptoms of this disease in the

majority of patients. More specifically, we now know that antipsychotic effectiveness is directly related to the drug's ability to block a specific subtype of dopamine receptor, called the D_2 receptor, although D_1 receptors are now also implicated. The greater the drug's ability to bind to D_2 receptors, the more clinically effective it seems to be. These observations offer strong support for the role of dopamine in psychosis. However, it remains to be determined why such medications require several days or longer before clinical improvement occurs, particularly when these drugs block most D_2 receptors within hours of their administration. Why is this? Let's examine the parts of this puzzle and see if there is a logical solution.

First, antipsychotic medications not only block dopamine receptors, they also increase plasma homovanillic acid (HVA), a metabolite of dopamine. This increase in levels of HVA is only seen during the first few days of antipsychotic treatment; then, plasma levels decline. However, it is not until the plasma levels of HVA decrease that clinical improvement is observed. There is some evidence that patients with higher levels of HVA prior to treatment respond better to antipsychotic medication than subjects with low pretreatment HVA levels.

Second, when animals are given dopamine receptor blockers, there is an initial increase in the release of midbrain dopamine, measured electrophysiologically as an increase in cell firing rates. This is followed by a long-term decrease in cell firing called depolarization inactivation. These results are consistent with the interpretation of changes in human plasma HVA (See Figure 8.2). In other words, dopamine antagonists may cause an initial increase in brain dopamine release followed by an increased metabolism of dopamine, which is followed by a decrease in cell activity, and therefore, a decrease in metabolism and correlated clinical improvement.

Finally, the strong affinity of newer antipsychotics to various serotonin and dopamine receptors may further explain the complex interplay among pharmacology, physiology and behavior. Antipsychotic medications that increase serotonin (see next section) may be involved in down-regulating brain dopamine.

Brain Dopamine Pathways

There are at least four major dopamine pathways (Table 8.2) in the brain where typical antipsychotics work. The anatomy and physiology of each is discussed in detail below.

Table 8.2 Major Dopamine Pathways

-
- mesolimbic tract
 - nigrostriatal tract
 - mesocortical tract
 - hypothalamic-pituitary (tuberoinfundibular) tract
-
- *Mesolimbic system:* Dopamine neurons located in the midbrain project axons to the limbic system where dopamine is released to regulate emotional behavior. Dopamine receptor supersensitivity in this area of the brain may cause the psychomotor agitation, sensitivity to sensory stimuli, delusions and hallucinations that often define schizophrenia. Stimulation or surgical ablation of some limbic system structures has been reported to produce behavioral and perceptual changes similar to those observed in schizophrenics. Finally, the mesolimbic system has a high concentration of dopamine receptors and high postmortem dopamine binding. Electroencephalograph, brain imaging, and cerebral blood flow studies reveal differences between schizophrenics and normal subjects. Taken together, there is good scientific evidence that the mesolimbic dopamine system is the key site of action for antipsychotic medications.
 - *Nigrostriatal system:* Dopamine neurons from the substantia nigra region of the midbrain project to the caudate-putamen of the basal ganglia or neostriatum. The terminals of these dopamine neurons project to other neostriatal neurons that are probably cholinergic. This pathway involves muscle control and movement. Damage to the nigrostriatal pathway or cell bodies within the striatum results in Parkinson's disease. Disturbances in the motor functions are a side effect of dopamine receptor blockade, similar to Parkinsonism. The basal ganglia are involved with slow voluntary movements. The extrapyramidal dopamine system regulates motor commands sent down from the cortex. Chronic blockade of dopamine receptors in this area results in extrapyramidal side effects (see below).
 - *Mesocortical system:* Dopamine pathways from the midbrain to the cortex relate to the sedative effects of antipsychotic medications.
 - *Hypothalamic-pituitary system:* The hypothalamus is in direct neural and circulatory contact with the pituitary gland and regulates the release of hormones. The hypothalamus, another limbic system structure, is also involved in emotion, eating, drinking, sex and pleasure. Many pathways from the hypothalamus use dopamine to communicate information and regulate physiology and behavior.

Atypical Antipsychotics

Second generation or “atypical” antipsychotics have fewer side effects, in part because they act as serotonin receptor antagonists – hence the term “atypical”. These medications block serotonin, dopamine and norepinephrine receptors. These medications have in many cases replaced the typical antipsychotics because of their fewer side effects. Examples of these newer medications are olanzapine (Zyprexa), olanzapine plus fluoxetine (Symbyax), quetiapine (Seroquel), risperidone (Risperdal), paliperidone (Invega), aripiprazole (Abilify), ziprasidone (Geodon), and clozapine (Clozaril).

Schizophrenia and Serotonin

There have also been studies suggesting that schizophrenia is related to the indolamine serotonin (5-HT). This notion was based on the observed fluctuations in urinary and cerebrospinal fluid levels of serotonin’s major acid metabolite, 5-HIAA. When schizophrenic symptoms were at their worst, the excretion of these compounds also increased, suggesting that increased serotonin turnover (release and metabolism) correlated with increased signs and symptoms of schizophrenia. When patients showed remission from schizophrenia, the urinary levels decreased. Analyses of many such studies have not always presented clear or uncomplicated findings, but taken together, these and related studies support a relationship between dysfunction of the brain serotonin system and schizophrenia.

Since many hallucinogenic drugs have a chemical structure similar to serotonin and one of the hallmarks of schizophrenia is hallucination, serotonin antagonists decrease many psychotic behaviors. Support for a serotonin theory of schizophrenia comes from clinical studies showing that when dietary amino acids such as tryptophan are given to patients previously treated with MAOIs, they make schizophrenic symptoms worse. Yet in normal individuals, tryptophan loading usually has a sedative-like effect. Why? Because in the brain, tryptophan is converted to serotonin, so the combination of extra precursor to the manufacturer of serotonin, coupled with a medication that inhibits the enzyme that metabolizes monoamines (MAOI) results in an increase in the bioavailability of brain serotonin and greater schizophrenia symptoms.

The role of serotonin in psychosis is now evident from the relative effectiveness of second generation or atypical antipsychotics. Unlike older typical

medications (see Table 8.1) that block dopamine receptors, these medications exert most of their clinical effectiveness by blocking specific classes of serotonin receptors (e.g., 5-HT_1 , 5-HT_2), rather than dopamine. Clozapine, for example, blocks more than 80 percent of 5-HT_{2A} receptors in the brain. Hence its effect is “atypical”. Also, unlike older (but still used) neuroleptics, medications like clozapine have far fewer adverse psychomotor and hematological side effects.

Where do Serotonin Antagonists Work?

Axons from the dorsal raphe nucleus project to the prefrontal cortex and striatum. These are areas of the brain most implicated in schizophrenia. Some evidence of a large increase in serotonin activity in the dorsal and ventral striatum suggests a hyper-serotonergic striatum in patients with schizophrenia.

Medical Consequences

Pharmacological treatment is always a cost-benefit equation. Although antipsychotic drugs are effective in reducing psychotic behavior in most cases, they have associated risks. These risks involve side effects caused by the drugs’ unwanted actions on dopamine pathways outside the mesolimbic system. Dopamine blockade, the primary action produced by antipsychotics, interrupts many of these functions, producing side effects. For example, dopamine is a prolactin-inhibiting factor that inhibits the release of the hormone prolactin. Since prolactin is normally involved in breast development and lactation (milk let-down), one side effect of antipsychotic medications is that they often cause breast enlargement in males (gynecomastia) and lactation in women. Other side effects of some antipsychotics include impaired ejaculation in men, loss of orgasm, abnormal menstrual cycles or infertility in women.

In addition to the endocrine side effects discussed above, the most profound consequence of long-term dopamine receptor blockade is on motor systems of the brain that are controlled in part by the extrapyramidal system. Many antipsychotic medications, such as haloperidol (Haldol), also bind to and block muscarinic or cholinergic receptors (causing anticholinergic effects, see Table 8.3). Generally, the more anticholinergic effects, the fewer extrapyramidal effects.

Table 8.3 Anticholinergic Side Effects

-
- dry mouth
 - blurred vision
 - glaucoma
 - mydriasis (pupil dilation)
 - constipation
 - urinary retention
 - tachycardia
-

Schizophrenia and Parkinson's Disease

We learned earlier that through the nigrostriatal dopamine system there was a relationship between antipsychotic drug use and Parkinson's disease. Since antipsychotics decrease the functional activity of brain dopamine and Parkinsonism is a disease characterized generally by a hypoactive dopamine system, it should not be surprising that antipsychotic medications produce Parkinson-like behaviors, including tremor and rigidity. Antipsychotic medications cause extrapyramidal side effects as well as a neuroleptic malignant syndrome (see below).

Extrapyramidal Side Effects

The pyramidal motor system is responsible for motor (muscle-control) movements and consists of long monosynaptic pathways from the cortex, where movement is initiated, to the spinal cord, where the pathways synapse with the motor neurons that ultimately innervate muscles. The extrapyramidal system is responsible for smoothing out motor movements and producing postural changes to accommodate movements. The extrapyramidal system consists of the cortex and several subcortical structures including the basal ganglia (caudate nucleus and putamen) and the globus pallidus. Several thalamic nuclei as well as brainstem reticular formation neurons also make up the extrapyramidal system. However, when the pyramidal system is damaged, motor movement can still be initiated, suggesting that the extrapyramidal system has a much more significant role in movement. Long-term use of typical antipsychotics produces four types of motor disorders involving the extrapyramidal system:

1. *Pseudoparkinsonism*: Symptoms include drooling, shuffling, pill-rolling movements of the fingers, tremor, and rigidity. The overall

symptomatology may be confused with depression and the side effects are severe enough to be a common cause of noncompliance with treatment. Extreme rigidity can be associated with fever and death (see Neuroleptic Malignant Syndrome, below). Symptoms develop 5 to 30 days after treatment and can be nearly identical to true Parkinson's disease.

2. *Tardive dyskinesia*: Symptoms include lip smacking, chewing, blowing, blepharospasm (squinting), bon-bon sign (twisting movement of tongue in cheek), and choreoathetoid (dancelike) movements of hands, fingers, toes and body. Tardive dyskinesia is prevalent in 15 to 20 percent of patients, with more among institutionalized patients. The symptoms may subside with discontinuation of treatment or be suppressed by decreasing the dose of the neuroleptic. Anticholinergics and dopamine agonists make symptoms worse.
3. *Akathisia*: This is the most common extrapyramidal side effect of antipsychotic treatment. The patient feels restless, and is unable to sit comfortably without continuous motor activity. Symptoms are often mistaken for agitation. It is most common in women and the symptoms develop within three months after the initiation of treatment, but often much earlier.
4. *Acute dystonic reactions*: These include facial grimacing or muscle spasms of the tongue, face, neck, and back. Symptoms are seen one to two weeks after treatment but may occur sooner.

Anticholinergic drugs are useful in treating the tremor and rigidity of pseudoparkinsonism but aggravate tardive dyskinesia.

Neuroleptic Malignant Syndrome and Other Adverse Effects

The neuroleptic malignant syndrome, a rare but life-threatening reaction to a neuroleptic medication, includes symptoms of severe rigidity, fever, autonomic nervous system dysregulation and elevated heart enzymes (e.g., creatine phosphokinase). The syndrome is twice as common among men as women. A full clinical picture develops rapidly once the syndrome starts. The neuroleptic malignant syndrome is potentially lethal and requires immediate medical treatment (e.g., discontinue treatment and administer dopamine agonists such as bromocriptine).

Newer antipsychotics (with little or no direct action as dopamine antagonists) have some advantages. Atypical antipsychotics have fewer

extrapyramidal side effects and fewer endocrine and other blood chemistry changes in comparison to older medications.

Prescribing doctors and their patients must monitor and be aware of the potential adverse effects of some neuroleptics.

Prenatal Effects of Antipsychotics

All medications have the potential to alter cell growth in the fetus during development, particularly during the early stages of pregnancy. At this time, there is insufficient data on the relationship between antipsychotic medications and fetal development. Women prescribed antipsychotic medications that are pregnant or who plan on becoming pregnant should notify their treating physician.

Forensic Considerations

Neuroleptic drug misuse is rare. These medications do not produce euphoric or a pleasurable sedation and they are not addicting. Although both typical and atypical neuroleptics can be detected in blood or urine long after use, the lack of compliance with taking these medications probably creates greater potential for impairment than steady-state therapeutic maintenance. Most antipsychotic drugs have fairly long elimination half-lives, frequently in the range of 20 to 40 hours; thus, they can be given in once-a-day doses or even less frequently if the half-life is longer. Metabolites of these drugs can be detected in the urine for long after drug discontinuation. The mere presence of these medications in blood or urine, coupled with a large number of potential side effects, should be interpreted in a forensic context with great caution and expertise.

Selected Bibliography

- Bach-y-Rita, P. (1994). Psychopharmacologic drugs: Mechanisms of action. *Science*, 264: 642–643.
- Baldessarino, R. (1990). Drugs and the treatment of psychiatric disorders. In: L. Goodman and A. Gilman (Eds.) *The pharmacological basis of therapeutics*, Eighth edition. New York: McGraw-Hill, pp. 383–435.

- Baselt, R. C. (2004). *Disposition of toxic drugs and chemicals in man*, Seventh Edition. Biomedical Publications, Foster City, CA.
- Buckley, P. and Meltzer, H. (1995). Treatment of schizophrenia. In: A. Schatzberg and C. Nemeroff (Eds.) *Textbook of psychopharmacology*. Washington, DC: American Psychiatric Press, pp. 615–640.
- Chiodo, L. A. and Bunney, B. S. (1987). Population response of midbrain dopaminergic neurons to neuroleptics: Further studies on time course and nondopaminergic neuronal influences. *Journal of Neuroscience*, 7: 629–633.
- Farde, L., Nordstrom, A. L., Wiesel, F. A., Pauli, S., Halldin, C. and Sedvall, G. (1992). Positron emission tomographic analysis of central D1 and D2 dopamine receptor occupancy in patients treated with classical neuroleptics and clozapine. *Archives of General Psychiatry*, 49: 538–544.
- Green, A. I. and Salzman, C. (1990). Clozapine: Benefits and risks. *Hospital and Community Psychiatry*, 41: 379–380.
- Hollandsworth, J. (1990). *The physiology of psychological disorders*. New York: Plenum Press.
- Julien, R. (1992). *A primer of drug action*. New York: Freeman Press, pp. 215–238.
- Leucht, S., Arbter, D., Engel, R. R., Kissling, W. and Davis, J. M. (2009). How effective are second-generation antipsychotic drugs? A meta-analysis of placebo-controlled trials. *Molecular Psychiatry*, 14: 429–447.
- Marder, S. R., Wirshing, W. and Van Putten, T. (1991). Drug treatment of schizophrenia: Overview of recent research. *Schizophrenia Research*, 4: 81–90.
- Pinel, J. (1989). *Biopsychology*. Needham Heights, MA: Allyn & Bacon.
- Roth, B. and Meltz, H. (2000). The role of serotonin in schizophrenia. In: F. Bloom and D. Kupfer (Eds) *Psychopharmacology – The fourth generation of progress*. American College of Neuropsychopharmacology.
- Sun, J. and Zhao, Z. (May 2010). Pathway-assisted investigation of atypical antipsychotic drugs and serotonin receptors in schizophrenia. *Biomedical Sciences and Engineering Conference (BSEC), 2010*, pp. 1–4, 25–26.
- Wallen, M. and Lorman, W. (2008). Special issues in patients with comorbid psychiatric and chemical dependency disorders. In: J. Brick (Ed.) *Handbook of the medical consequences of alcohol and drug abuse*. Haworth Press; Taylor & Francis Group, pp. 579–621.

Stimulants: Drugs That Make Us High

9

Stimulants range from caffeine in coffee to strong hallucinogenic stimulants. Cocaine, considered by most to be one of the world's most addicting drugs, and along with amphetamine has powerful euphoriant effects and a high potential for abuse. Stimulants also have some medical use applications. In contrast, the high abuse potential and euphoric effects of cocaine causes it to be a major problem from the upper middle class (where the powder is mainly used), to the crime-ridden economically-disadvantaged population (where it is mainly smoked as crack or freebase). Amphetamines are legal prescription drugs that have gone awry in over-prescribed uses for attention-deficit hyperactivity disorder (ADHD), obesity and narcolepsy. More potent stimulants, such as methamphetamine have even more serious medical and psychological consequences but remain popular. Each of the stimulants discussed stimulate the nervous system in different ways and most have a high potential for harm.

History of Stimulant Use

The use of some stimulants is not new. In South America, indigenous persons chewed coca leaves (the source of cocaine) for their psychoactive effects for thousands of years and its use is an intricate part of their culture. The chewing of coca leaves has a social use similar to “coffee breaks” in the US and other countries. In China about 1000 BC, caffeine from tea was popular while in Europe at the turn of the last century, the use of coca leaves was recommended for travelers, hikers, and soldiers because it suppresses appetite

and is a mild stimulant. Today, the three most prevalent stimulants are cocaine, amphetamines and caffeine.

In the United States cocaine was used in soft drinks (Coca-Cola) and wines for many years, until 1914 when its use was stopped by the Harrison Narcotic Act. Cocaine's legal therapeutic use today is restricted to local anesthesia for eye surgery. Related analogues of cocaine (e.g., Procaine, Lidocaine, Novocain) are used in general dentistry and minor surgery as local analgesics. Today's cocaine is much more potent and has a greater potential for abuse, addiction, and toxicity. Even with the known consequences for addiction and toxicity, current data indicates that in the US, 1.5 percent of 12th grade students have used cocaine in the last 12 months. Among people aged 12 or older, about 1.7 percent or about 4.8 million people aged 12 or older report using cocaine in the last year whereas methamphetamine use is about half that. It is estimated that 0.5 percent or 1.4 million people reach diagnostic criteria for cocaine use disorder.

First synthesized in 1897, amphetamines are historically relatively new. Like cocaine, amphetamines also have medical applications and are used recreationally. There are different formulations of amphetamine, designated levo-amphetamine (or *l*-amphetamine) and dextro-amphetamine (or *d*-amphetamine). Amphetamine is a derivative of phenethylamine, a neurotransmitter and amino acid precursor for the dopamine. The chemical structure of these stimulants is very similar to neurotransmitters in the brain, such as norepinephrine and in some cases, differs by the position of one or more hydrogen atoms in the core structure. Amphetamine forms the backbone for other stimulants such as methamphetamine, and its derivatives such as methylenedioxymethamphetamine (MDMA).

Although they are each similar, their effects and applications vary. For example, amphetamine (as Adderall) is used to treat obesity, narcolepsy, hypotension, as well as attention deficit hyperactivity disorder (ADHD). Methylphenidate (e.g., Ritalin, Concerta), a derivative of phenylethylamine, is also used to treat ADHD presumably because it inhibits overactive brain areas that mediate the symptoms of ADHD. Since amphetamine is also effective, to a degree, in alleviating depression, increasing attention and memory performance and learning in general, a child may more easily adjust to the environment if treated with amphetamine analogs like Ritalin. Although amphetamines are also used to treat uncontrollable sleep episodes, obesity and other ailments, it is not the first drug of choice and has been replaced by safer, more effective and less addictive medications.

Cocaine and Amphetamine: Differences and Shared Similarities

Cocaine is a powerful, but short-acting, central nervous system stimulant. Once in the body, cocaine concentrations are metabolized to half their maximum amount in about one hour compared with methamphetamine concentrations that are metabolized to half their concentration after 12 hours, based on their half-life (see Chapter 3 and 18). Cocaine is extracted from the leaves of *Erythroxylum coca*, a shrub-like tree that grows abundantly in the mountains of Peru, Colombia, and Bolivia. It is used as a mild stimulant by indigenous people in that region, medically as a local anesthetic and by drug abusers for its potent stimulant effects.

There is a significant difference in potency and effect between the coca leaf, which is chewed for its mild stimulant effects and either pharmaceutical grade or street grade cocaine. That difference begins with an extraction process. The waxy elliptical leaves of the plant are soaked in kerosene and sulfuric acid to form a coca paste (cocaine sulfate). The addition of hydrochloric acid forms powdery flakes or rocks of cocaine hydrochloride. When cocaine is chemically altered by removing its chemical base, crack (freebase cocaine) is formed.

In contrast to cocaine, amphetamines are man-made in the laboratory and can be synthesized by different chemical methods. One common method involves the Leuckart reaction that occurs when aldehydes or ketones (two related organic compounds) are heated. This reaction produces amines that through various chemical reduction, extraction and distillation processes used to synthesize amphetamine. The details of this process are beyond the scope of this book but whether it is an organic, naturally occurring stimulant or a synthetic, cocaine, amphetamine and other stimulants are drugs that produce effects similar, and in some cases identical, to the normal actions of the sympathetic nervous system. Stimulants literally turn on your nervous system!

Because of the ability of these drugs to increase heart rate and blood pressure, dilate the pupils, and increase arousal, they are sometimes referred to as sympathomimetics because they mimic the effects of the sympathetic nervous system (described in Chapter 4). Street cocaine goes by many names, including coke, C, snow, blow, toot, nose candy and the lady, but they all refer to one drug: cocaine hydrochloride. Amphetamine is a synthetic stimulant with longer lasting effects as compared with cocaine or methamphetamine. Amphetamines are formulated as pills, in capsules or as a powder and may

have a crystalline like appearance, hence the use of the slang term “ice”. Other slang terms are Bennies, Black Beauties, Crank, Speed and Uppers.

Stimulants often have a remarkable molecular similarity to neurotransmitters and hormones outside the brain, which explains their ability to mimic peripheral and central nervous system effects. Figure 9.1 shows the molecular structures of cocaine, amphetamine and two neurotransmitters.

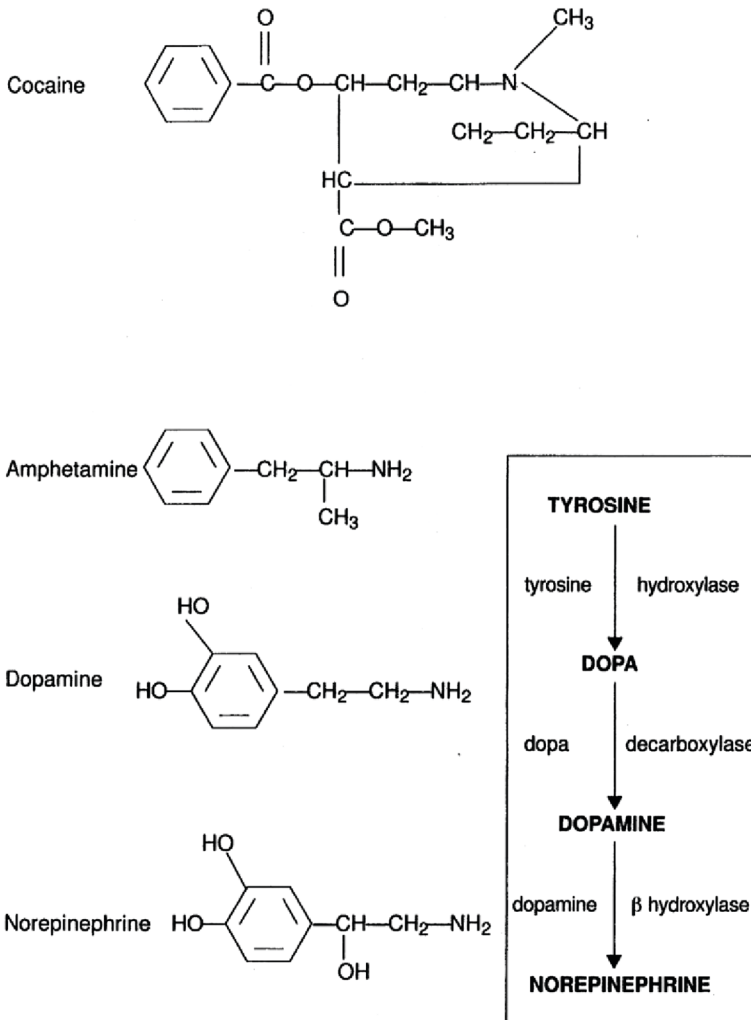


Figure 9.1 Biochemical structures of various sympathomimetics. Insert illustrates biosynthesis of catecholamines

Other Stimulants of Interest

Cathinone

Cathinone is also known as benzoylethanamine or beta-keto-amphetamine is a stimulant found in the khat plant. This plant is believed to have originated in Ethiopia and has been cultivated in and around the region for thousands of years. It is chewed by farm workers much like coca leaves to reduce fatigue and by others for its pleasurable stimulating effects. Synthetic cathinone products such as “bath salts” are among the list of ever changing “new psychoactive substances” (NPS). Cathinone is a Schedule I Drug under the US Drug Enforcement Agency and is illegal in the US and Europe, but not in many regions in Africa. Cathinones are similar to amphetamines, cocaine and MDMA with similar psychoactive effects, mechanism of action, health risks and addictive properties.

Caffeine

The last category of stimulants to be discussed is xanthines, the most well known of which is caffeine. Caffeine is the most widely used drug on earth and in the US it is estimated that more than 90 percent of adults consume caffeine regularly. Xanthines are nitrogen based organic compounds derived from plants (e.g., cocoa bean). Xanthines are also found in the body as a result of purine metabolism. Purine is one of the building blocks in cells to make DNA and RNA. Although caffeine is widely used throughout the world, its use rarely results in the medical, psychosocial and other harmful effects of other stimulants but high doses can produce adverse health effects. Xanthines are often used in bronchodilators (for asthma) and have mild stimulant properties. Compounds in this category include caffeine, theophylline and theobromine. Caffeine comes from coffee beans, which is a good source of this drug and the most powerful of the xanthine stimulants. As with other stimulants, caffeine exerts sympathomimetic effects.

Tea contains both caffeine and theophylline and cocoa (chocolate) contains smaller amounts of caffeine and theobromine. The nut of the cola tree also contains caffeine, which explains the brand name Coca-Cola. This soft drink was not always soft and originally contained both cocaine (coca) and cola

(caffeine). Today, cola drinks contain about one third the amount of caffeine found in a cup of coffee and no cocaine.

Administration, Absorption, Distribution and Elimination of Stimulants

The major routes for administering cocaine and amphetamines are: absorption (oral and nasal), injection and pulmonary.

Absorption (oral)

Although all stimulants can be absorbed through the gastrointestinal system, oral administration of cocaine is more common outside of the US. Cocaine is extracted from the leaves of *Erythroxylum coca*. When the leaves are chewed, small amounts of cocaine are extracted into the saliva and absorbed into the circulation from the membranes in the mouth. Very little is known about coca leaf abuse or addiction in this culture and it is difficult to diagnose and compare cocaine-related problems between industrial-technocratic societies and agrarian societies. In any event, the chewing of coca leaves is not popular in the United States, where the leaf form of the plant is rarely seen. In the United States and in many other countries, the most common form of stimulant administration is insufflation. Other stimulants, such as amphetamine and *d*-methamphetamine are available in normal and prolonged release tablets for oral use. After oral use, peak concentrations are reached about two to three hours after ingestion for amphetamines.

Insufflation (nasal)

In the US, the most common route of stimulant administration is “insufflation”, more commonly known as “snorting”. During insufflation, one end of a straw, rolled dollar bill or similar tube-like device is placed in the nose while the opposite nostril is pinched closed. The user then moves the tube along a prepared “line” of cocaine or amphetamine, for example. By inhaling quickly and deeply, the powder is drawn up the tube and into the posterior portion of the nasal septum. Within about three minutes, the drug is absorbed

through the nasal epithelium, into the circulation, and then to the brain. Peak concentrations are reached in about 30 minutes (cocaine).

Injection

Cocaine, amphetamine hydrochloride and other amphetamine-related stimulants are water soluble, meaning it is easily mixed with water (or some other fluid) and can be injected through a needle with a syringe. The most effective and common type of injection is intravenous. When injected intravenously, the drug gets to the brain in about 15 seconds and the “rush” begins and peak concentrations are reached rapidly after that.

Pulmonary

Some forms of cocaine, such as crack-cocaine are smoked. Crack is a harder, chunky, off-white form of cocaine that derives its name from the “crackling” sound made when smoked in a pipe. Smoked crack-cocaine is absorbed immediately into the blood supply through the lungs. The rush from smoking crack-cocaine is very rapid, as the drug gets to the brain in about five seconds. Although the onset is very fast, the effects last only about five to ten minutes. The subjective effects of the high then diminish quickly, until more drug is administered. Paste may also be smoked in a cigarette or joint, although this is not very common in the United States.

Stimulants are rapidly distributed into the circulation from pulmonary and injection administration and relatively rapidly from insufflation.

Elimination

Cocaine and amphetamines are metabolized, primarily in the liver mostly to inactive metabolites, such as benzoylecgonine for cocaine. The elimination half-life is approximately 0.7–1.5 hours whereas the half-life of amphetamine varies greatly from about 11 hours or longer depending on the form of amphetamine and individual physiological differences. Amphetamine metabolism also results in the formation of psychoactive metabolites, including norephedrine, that extend the effects of the drug. The range of half-lives may

vary considerably and is related to route of administration, formulation of the stimulant and to some degree, drug concentration. The metabolic half-life of and duration of effect may be extended up to several hours with chronic use.

Neuropharmacology of Cocaine and Other Stimulants

Cocaine

Along with other drugs of abuse, cocaine exerts its neuropharmacological effect by activating brain dopamine. The primary mechanism through which mesolimbic dopamine is activated by cocaine is by blocking the reuptake of dopamine release from the neurons terminating in the nucleus accumbens. Cocaine also inhibits reuptake of serotonin and norepinephrine by binding to their transporters that normally remove these neurotransmitters from the synapse and returns it to the presynaptic neuron. Since dopamine, norepinephrine and serotonin remain in the synapse, these neurotransmitters continue to contact receptors to exert its effects. Amphetamine also increases the functional activity of dopamine in a different way. This elevation of dopamine activity and the anatomical regions of the brain involved are far greater than for other reinforcers such as food or sex. Perhaps even more than any other addicting drug, the stimulation of mesolimbic dopamine reward/pleasure pathways result, what many users described, as an unparalleled state of well-being and euphoria.

While dopamine reigns supreme as the neurochemical of greatest pharmacological significance in cocaine intoxication, non-dopaminergic neurons and circuits and other neural systems are also involved in the development of addictive behavior. For example, chronic exposure to cocaine causes a decrease in brain serotonin, a neurochemical involved in depression. It may be that memories of the “well-being” associated with earlier cocaine use is part of the cycle of addiction and more drug is then craved.

Cocaethylene

Cocaethylene is a novel substance that is rapidly formed when cocaine and alcohol are both present in the body. Cocaethylene has stimulant properties that are similar to cocaine, including increased mental alertness, subjective

excitement and the feeling of being “high” but also increases heart rate, blood pressure and body temperature. Both cocaethylene and cocaine block the reuptake of dopamine and it is believed that cocaethylene contributes to the pleasurable and reinforcing effects of cocaine. Cocaethylene has a longer half-life than cocaine and probably extends the biobehavioral effects of cocaine through the same brain dopamine systems.

Amphetamines

Amphetamine and related compounds (e.g., methamphetamine (Methedrine), dextroamphetamine (Dexedrine) and methylphenidate (Ritalin), are also potent stimulants, with similar pharmacological actions to cocaine. Amphetamine exerts its biobehavioral effects by potentiating the release of brain mesolimbic dopamine, as well as norepinephrine, and serotonin. As with cocaine, this results in an increase in the functional activity of these neurotransmitters and increases whatever biobehavioral effects they produce on the brain and behavior.

Xanthines

Pharmacologically, caffeine acts as a general cellular stimulant. The primary mechanism of action for caffeine involves the inhibition of phosphodiesterase, the enzyme that breaks down cAMP. Increasing available cAMP increases the phosphorylation of proteins in the membrane and changes the functional activity of the neuron (see Figure 9.2). Caffeine also acts as an adenosine receptor antagonist. This action produces a range of effects including stimulation of brain dopamine activity normally inhibited by adenosine. Blocking adenosine receptors stimulates brain dopamine.

Biobehavioral Effects of Stimulants

Physically, cocaine and amphetamine relieve fatigue, increase heart rate, respiration, temperature, and blood pressure, cause pupil dilation (mydriasis), and is a local anesthetic (cocaine). Table 9.1 lists some of the more common biobehavioral effects of stimulants (cocaine and amphetamine). Intoxication does not mean impairment as many of the symptoms of stimulants are

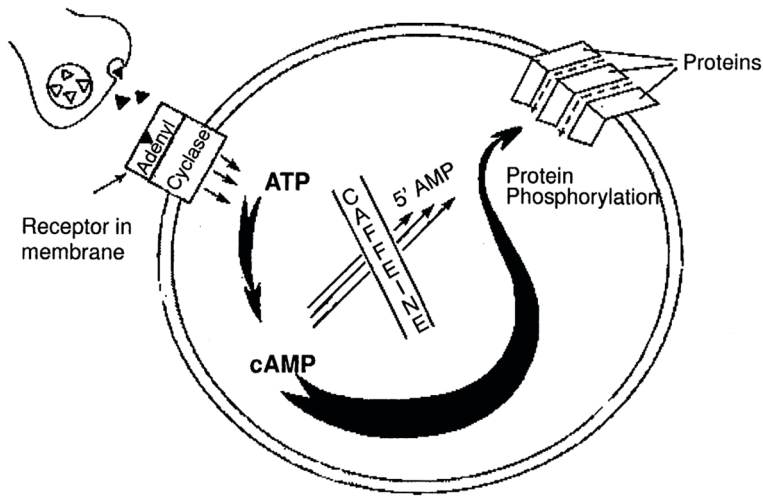


Figure 9.2 Neuropharmacological action of caffeine

Table 9.1 Associated Biobehavioral Effects of Stimulants

Intoxication	Overdose
Euphoria, high sense of well-being and confidence, energetic, garrulous (overly talkative), insomnia, cannot remain still, increased alertness, tachycardia, hypertension, pupil dilation, hyperthermia.	Dystonia (muscle tremor, twitching), severe hypertension, dyskinesia (decreased voluntary and increased involuntary movements), compulsive harmful stereotypic movement, nausea or vomiting, cardiac arrhythmias, confusion, agitation, diaphoresis, chills, seizure, coma

actually beneficial or the desired outcome from use. High doses or individual sensitivity to stimulants may result in less subjectively desirable, and more likely harmful or even fatal results.

Drinking coffee or tea (which has about half the amount of caffeine) is a common morning ritual for millions of people. The physiological effects of caffeine include increasing alertness, wakefulness, heart rate, blood pressure, diuresis and decreasing fatigue. For most people, these effects are relatively modest and consistent with expectations from prior use. In higher doses, the biobehavioral effects of caffeine intoxication include nervousness, cardiac arrhythmias, rambling thoughts, insomnia, muscle twitching, or tremor. At doses well beyond what most people drink during the course

of the day, caffeine can cause disorientation and a psychotic-like state, but this is rare.

While intoxicated by stimulants like cocaine or amphetamine, many people engage in repetitive, almost compulsive motor activity such as rearranging furniture or the contents of pocketbooks, wallets, etc. Some users state that resisting such urges is uncomfortable and aversive. In high doses, repetitive or stereotypic behavior such as scratching or picking at the skin with such intensity that it breaks the skin and causes harm (e.g., infection).

Some cocaine users drink alcohol to produce various types of cognitive performance changes. With chronic use of both drugs, alcohol seems to increase the body's sensitivity to cocaine. This effect may be due to the production of cocaethylene, which has a half-life almost three times longer than cocaine. Cocaethylene also appears to block the reuptake of dopamine to produce its pharmacological effects and may exacerbate the effects of alcohol.

Tolerance and Dependence

Tolerance and dependence develop to varying degrees for all stimulants. Seventy years ago, cocaine was not widely believed to be an addicting drug because the discontinuation of chronic cocaine use did not produce typical physical withdrawal symptoms such as those observed with drugs like alcohol or heroin. It is now well known that cocaine is extremely addictive. The euphoria produced by crack-cocaine, for example, is so intense and the change in brain state so great, that craving for the drug starts to develop after only a few trials. Tolerance develops rapidly to the intoxicating effects of amphetamines but long-term chronic use is less common than binges or "runs" of several days.

Cocaine addiction (dependence) is not difficult to understand. Psychologically, cocaine is a potent mood elevator that produces (through changes in brain chemistry) unparalleled euphoria, exhilaration, increases alertness, feelings of well being and confidence. It also decreases tension, self-doubt, and appetite. The laws of learning clearly predict that the elimination of an aversive state, coupled with a newfound euphoria, makes for a behavior likely to be repeated. Cocaine produces these effects by acting directly on dopamine rich pleasure centers in the brain such as the medial forebrain bundle (discussed in Chapters 2 and 16).

Some people use cocaine once or twice out of curiosity or some other reason and never use the drug again ("cocaine abusers"). Others seek

treatment when their pattern of abuse and dependence leads to legal, financial, vocational, medical, psychological, or other problems. There is no single treatment for cocaine addiction. As with other drugs, overcoming denial of the problem and entering treatment are the first steps toward recovery. Some experts believe that cocaine is the most addicting drug of all.

Amphetamines are indeed highly addicting (dependence-producing). However, the opinion of those who treat attention deficit disorder (ADD) is that giving ADD-diagnosed children amphetamines such as Dexedrine and Ritalin does not enhance the likelihood of addiction in those children.

Caffeine

Caffeine produces relatively mild physical withdrawal (headache, gastrointestinal problems, sleep disturbances) and low-degree tolerance. Chronic high doses of caffeine are likely to produce clinically significant distress. Although the World Health Organization includes a diagnosis of Caffeine Dependence Syndrome, the American Psychiatric Association does not, but it does recognize Caffeine Use Disorder in the current DSM-V.

Medical Consequences of Stimulants

Psychological Consequences

As the drug wears off, the euphoria is followed by a physiological and psychological depression called a “crash”. The crash includes rebound sleep, clinical depression, and autonomic dysfunction. About 95 percent of the symptoms are emotional, not physical. Crack smokers as well as intravenous cocaine “shooters” report that after the rush there is an intense craving for more drug. These effects are probably associated with the depletion of dopamine and serotonin caused by using the drug over a prolonged period of time.

Repeated use of stimulants results in insidious personality changes. Abusers become short-tempered, suspicious, and have difficulty concentrating. Among cocaine abusers, the inability to enjoy previously pleasurable activities, including sex is well known. This pleasureless state, called anhedonia, may last for many months after drug use stops. Schizoid behavior and personality changes may also develop. Frequent high doses of cocaine can result in cocaine psychosis. The drug-induced psychotic has delusions,

paranoia, and may react violently against real or imagined persecution, which is similar to some forms of schizophrenia. Visual, tactile (“coke bugs”), and auditory hallucinations may last days, weeks, or months. Also, like psychotics, stimulant abusers have very little insight into their problem.

Chronic use of amphetamine produces a toxic psychosis or schizophrenia characterized by confused, disorganized behavior, stereotypy, paranoia, hallucinations, and delusions. Weight loss and skin ulcers from injection infections or skin picking (dermatillomania) may also be observed in the chronic amphetamine and cocaine users.

Heart Attacks, Convulsions, and Death

Cocaine’s sympathomimetic effects include increases in heart rate and blood pressure (it constricts blood vessels). One intravenous cocaine user reported that he knew when he had good cocaine because he felt as though his heart was going to explode through his chest. Cardiomyopathy, dysrhythmias, irritation of cardiac tissue and hypertension are potential consequences of long-term use of stimulants.

Neurological

Cocaine and other stimulants increase risk for stroke (subarachnoid, intracerebral hemorrhage and ischemic infarcts), convulsions and headache. Most of these effects are probably related to the hypertensive (high blood pressure) effects of the drug. Long term use of cocaine or crack-cocaine can result in choreiform movements. These involuntary movements, often described as “crack-dancing” reflect long-term nervous system damage.

Pulmonary Effects

Smoking crack-cocaine causes cough and shortness of breath due to the local tissue irritation but these effects are generally not signs of pulmonary damage. However, repeated smoking of free-base can cause pulmonary edema and lung diseases. Massive doses or bingeing on cocaine can result in respiratory paralysis, heart attacks (especially in men under 40 years of age), convulsions and death.

Perforated septum from “snorting”, and HIV infection (from shared needles, if the drug is injected) are also deleterious consequences of cocaine abuse. Massive doses or bingeing on cocaine can result in respiratory paralysis, heart attacks (especially in men under 40 years of age), convulsions and death.

Other Systems

Insufflation of cocaine can cause perforation and collapse of the nasal cartilage (septum) that separates the air passages in the nose. Damage to the cornea of the eye has also been reported as “crack-eye” which may include bacterial and fungal infections of the cornea. It is not known what causes these corneal abrasions but they do not seem related to external physical trauma. Muscle breakdown (rhabdomyolysis) is another consequence of long-term cocaine/stimulant use.

Chronic stimulant use is also harmful to the oral cavity. Dental erosion and abrasion from bruxism (tooth grinding) are well reported as is xerostomia. Severe xerostomia caused by decreased saliva production (dry-mouth). Since saliva neutralizes acids and protects the gums from bacteria, it provides important protection to the teeth. When this process is reduced by stimulant use, cavities and periodontal complications follow. “Meth mouth” is a well known and serious adverse medical consequence of chronic methamphetamine use.

Stimulants and the Fetus

Currently, it is estimated that about 5 percent of pregnant women use one or more addictive drug during their pregnancy and about 750,000 neonates are exposed to cocaine through the mother’s use of the drug. When the mother uses cocaine, the drug’s low molecular weight and high solubility enables it to pass freely through the placenta. The fetus is particularly sensitive to cocaine because, in contrast to the mature organism, low levels of fetal enzymes are unable to metabolize the drug and the fetus receives the full effect of the dose. This problem is made worse when the mother binges and high blood levels are obtained within minutes.

The effect of cocaine on fetal development is better studied than other stimulants, probably because it is popular and more available than other stimulants. Cocaine acts as a vasoconstrictor (constricts blood vessels and

decreases blood flow), which in turn, decreases the blood oxygen supply to organs. In both animal and human studies, fetal hypoxia (lack of oxygen) is associated with growth retardation and congenital malformations. In humans, in-utero cocaine exposure coupled with other factors results in growth retardation, decreased head size, and increased risk for abruptio placentae, in which there is a premature separation of the placenta from the uterus, premature birth, and in some cases, death. Cocaine's effect on fetal heart rate and blood pressure may also contribute to cerebral hemorrhaging, infarctions, and other pregnancy complications. Unlike alcohol, cocaine-induced congenital malformations in humans are rare and not well documented. The term "fetal vascular disruption" has been offered to explain the array of observed cocaine-related malformations.

At birth, babies born of cocaine-abusing mothers are smaller in size, usually premature, require neonatal intensive care, have poor visual processing of faces and objects, abnormal sleep patterns, tremors, poor feeding, and transient central nervous system irritability. Although we know a lot about the physiological effects of cocaine and how those affects may affect fetal development, these findings should be interpreted cautiously for three reasons: 1) not all researchers have found a relationship between in-utero cocaine exposure and physical or behavioral including cognitive consequences; 2) many of the effects reported may be due to concomitant use of alcohol, nicotine or other drugs, and poor nutrition, and 3) studies that find results of in-utero cocaine exposure are more likely to submit for publication than studies that do not find such results. The long-term effects in these babies as they grow are still being investigated.

Forensic Considerations

Crimes of all types frequently involve drugs, including cocaine. However, the interpretation of such findings must be done with an understanding of what is being reported. Research of deaths in New York City, for example, indicate that murder victims are 10–50 times more likely to be cocaine users. Recent cocaine use is indicated in about one third of all victims. Clearly, the pharmacological effects of cocaine do not cause people to be murdered but the behavioral effects and social environment of cocaine users likely contribute to high-risk situations.

Driving

Laws against driving under the influence of alcohol usually include other drugs (e.g., stimulants). While stimulants and other psychoactive drugs are clearly represented in fatal accidents, the hazards posed by these drugs to users have been the subject of considerable debate within the scientific community. Although cocaine and other stimulants have been found to be present in a large number of motor vehicle crashes most studies of cocaine in crime involve either urine testing which typically detects inactive cocaine metabolites and does not reflect the state of intoxication at the time of an accident or fatal crash. Although the effects of stimulants on human physiology and behavior are well known, controlled real-world studies of driving performance are largely lacking. Even so, it can be concluded that except for some conditions, such as high doses or withdrawal from cocaine, a causative relationship between acute cocaine intoxication and driving is equivocal.

The US Department of Transportation reached similar conclusion in summarizing the state of knowledge regarding drug-impaired driving. Noting that significant new information about the role of several classes of drugs in traffic crashes has been acquired,

the role of drugs as a causal factor in traffic crashes involving drug-positive drivers is still not understood. Drug risk factors are still not known with acceptable precision, with some evidence suggesting little or no increase in crash risk at drug levels being detected by current chemical test procedures.

The US DOT concluded “CNS stimulants (including cocaine and amphetamines) were associated with either no increased risk factor (cocaine) or even a decreased risk factor (other stimulants)” (US Department of Transportation 2003).

This does not mean that driving under the influence of stimulants is not without risk, particularly when high doses are involved. The behavioral effects of stimulants such as repetitive, focused, and impulsive actions are likely to impair the performance of complicated tasks such as driving an automobile. Even so, it has been argued that risk-taking behaviors or impulsivity are personality characteristics of the user and not characteristics of drug use. Longer lasting stimulants (e.g., amphetamines) as compared with short acting stimulants (e.g., cocaine) may give a better window to study the effects of

stimulants on driving. Drivers under the influence of methamphetamine drift out of lane, weave, speed and engage in risk taking and are involved in high-speed crashes. Even so, causality to actual highway crashes remains problematic. Even so, the CNS arousal from stimulants may increase focus and concentration (which may improve driving under some conditions) but at the expense of “tunnel vision” and loss of peripheral acuity.

Finally, the consumption of alcohol is well known to impair driving and related divided attention task. The consumption of alcohol with highly caffeinated energy drinks is popular, particularly among younger drinkers. Most people reach a point of intoxication and stop drinking. However, the combined use of highly caffeinated energy drinks reduces the fatigue that follows alcohol use, thereby removing a potential limiting factor in alcohol use and increasing the risk for continued drinking and even greater impairment and increased risk for a motor vehicle crash or related injury.

Selected Bibliography

- Al-Motarreb, A., Baker, K. and Broadley, K. (2002). Khat: Pharmacological and medical aspects and its social use in Yemen. *Phytotherapy Research*, 16(5): 403–413.
- Barnes, D. (1988). The biological tangle of drug addiction. *Science*, 241, 415–417.
- Barnes, D. (1988). Drugs: Running the numbers, *Science*, 240, 1729–1731.
- Baselt, R. (2004). *Disposition of toxic drugs and chemicals in man*. 7th Edition, Foster City, CA: Biomedical Publications.
- Bhuvaneswar, C., Chang, G., Epstein, L. and Stern, T. (2008). Cocaine and opioid use during pregnancy: Prevalence and management. *Primary Care Companion to the Journal of Clinical Psychiatry*, 10(1): 59–65.
- Brick, J. (1991). Facts on Cocaine/Crack. Rutgers University Center of Alcohol Studies, Resource Center and Clearinghouse.
- Brick, J. (1988). *Drugs and the brain: An introduction to neuropharmacology*. New Brunswick, NJ: Rutgers University Center of Alcohol Studies Publication Division.
- Brown, R. (1989). Pharmacology of cocaine abuse. In: K. K. Redda, C. A. Walker and G. Barnett (Eds), *Cocaine, marijuana, designer drugs: Chemistry and pharmacology*. Boca Raton, FL: CRC Press, pp. 39–52.
- Byck, R. (1987). The effects of cocaine on complex performance in humans. *Alcohol, Drugs and Driving*, 3(1): pp. 9–12.
- Cain, M., Bornick, P. and Whiteman, V. (2013). The maternal, fetal and neonatal effects of cocaine exposure during pregnancy. *Clinical Obstetrics and Gynecology*, 56(1): 124–132.
- Clouet, D., Asghar, K. and Brown, R. (1988). *Mechanisms of cocaine abuse and toxicity*. Rockville, MD: National Institute on Drug Abuse, NIDA Research Monograph 88.

- Coghlan, M. and Macdonald, S. (2010). The role of substance use and psychosocial characteristics in explaining unintentional injuries. *Accident Analysis & Prevention*, 42: 476–479.
- Giros, B., Jaber, M., Jones, S., Wightman, R. and Caron, M. (1996). Hyperlocomotion and indifference to cocaine and amphetamine in mice lacking the dopamine transporter. *Nature*, 379: 606–612.
- Hutchings, D. (1993). The puzzle of cocaine's effects following maternal use during pregnancy: Are there reconcilable differences? *Neurotoxicology and Teratology*, 15: 281–286.
- Johnson, L., O'Malley, P. and Bachman, J. (1996). *Monitoring the future study 1975–1996*. Rockville, MD: USDHHS, National Institute on Drug Abuse.
- Johnston, L. D., O'Malley, P. M., Bachman, J. G. and Schulenberg, J. E. (2011). *Monitoring the future national survey results on drug use, 1975–2010: Volume II, College students and adults ages 19–50*. Ann Arbor: Institute for Social Research, The University of Michigan.
- Jones, A. W. (2019). Forensic drug profile: Cocaethylene. *Journal of Analytical Toxicology*, 2019: 1–6.
- Lakosko, J., Galloway, M. and White, F. (Eds) (1992). *Cocaine pharmacology, physiology and clinical strategies*. Boca Raton, FL: CRC Press, pp. 372–373.
- Lambert, B. and Bauer, C. (2012). Developmental and behavioral consequences of prenatal cocaine exposure: A review. *Journal of Perinatology*, 32(1): 819–828.
- Langenbucher, J., McCrady, B., Brick, J. and Esterly, R. (1993). *Socioeconomic evaluations of addictions treatment, President's Commission on Model State Drug Laws*. Washington, DC: The White House.
- Macdonald, S., Anglin-Bodrug, K., Mann, R., Erickson, P., Hathaway, A., Chipman, M. and Rylett, M. (2003). Injury risk associated with cannabis and cocaine use. *Drug and Alcohol Dependence*, 72: 99–115.
- Meredith, S., Juliano, L., Hughes, J. R. and Griffiths, R. (2013). Caffeine use disorder: A comprehensive review and research agenda. *Journal of Caffeine Research*, 3(3): 114–130.
- National Institute of Drug Abuse (NIDA) Research Report (2021).
- NIDA (National Institute on Drug Abuse) (2018). *DrugFacts: Synthetic cathinones*.
- O'Brien, M., McCoy, T., Rhodes, S., Wagoner, A. and Wolfson, M. (2008). Caffeinated cocktails: Energy drink consumption, high-risk drinking and alcohol-related consequences among college students. *Academic Emergency Medicine*, 15(5): 453–460.
- Ramaekers, J., Kuypers, K., Bosker, W. et al. (2012). Effects of stimulant drugs on actual and simulated driving: Perspectives from four experimental studies conducted as part of the DRUID research consortium. *Psychopharmacology (Berl)*, 222(3): 413–418.
- Rees, T. and Levine, R. (2008). The adverse effects of alcohol and drug abuse in the oral cavity. In: Brick, J., (2008). *Handbook of the medical consequences of alcohol and drug abuse*, 2nd Edition. Haworth Press/Taylor Francis Group, pp. 565–578.

132 Stimulants: Drugs That Make Us High

- Romano, E. and Voas, R. E. (2011). Drug and alcohol involvement in four types of fatal crashes. *Journal of Studies on Alcohol and Drugs*, 72: 567–576.
- Ross, E., Graham, D., Money, K., Stanwood, G. (2015). Developmental consequences of fetal exposure to drugs: What we know and what we still must learn. *Neuropsychopharmacology*, 40(1): 61–87.
- Rothman, B., Baumann, M., Prisinzano, T. and Newman, A. (2008). Dopamine transport inhibitors based on GBR12909 and benztropine as potential medications to treat cocaine addiction. *Biochemical Pharmacology*, 75(1): 2–16.
- Siegel, R. K. (1987). Cocaine use and driving behavior. *Alcohol, Drugs and Driving*, 3(1): 1–7.
- Silber, B. and Swann, P. (2005). The effects of dexamphetamine on simulated driving performance. *Psychopharmacology*.
- Tardiff, K., Marzuk, P., Leon, A., Hirsch, C., Stajic, M., Portera, L. and Hartwell, N. (1994). Homicide in New York City: Cocaine use and firearms. *JAMA*, 272: 43–46.
- US Department of Transportation (2003). State of Knowledge of Drug-Impaired Driving. (DOT HS 809 643).
- US DHHS (2023). National Survey on Drug Use and Health Results Detailing Mental Illness and Substance Use Levels in 2021.
- Widmark, E. (1981). *Principles and application of medicolegal alcohol determination*. CA: Biomedical Publications, pp. 47–82.

Alcohol: The Socially Accepted Addictive Drug

Alcohol is perhaps the world's oldest known drug. It has historically been known as a food, a nutrient, a palliative and (today) a drug. It is one of the few drugs that do not act at a specific receptor site of its own in the body. In this chapter, we will learn that alcohol has almost as many effects outside the brain as within, yet its use is primarily for its effects on the central nervous system. It is toxic to almost everything, including the liver, heart, brain, gut, pancreas, germs, and the developing fetus – yet people still drink gallons of it a year. We know more about this drug than other psychoactive drugs, yet we still do not know all of the mechanisms through which it works to produce intoxication and addiction but we do know a lot about the consequences.

What is Alcohol?

There are many different types of alcohol, but the three most common ones include ethyl alcohol, (ethanol), methyl alcohol (methanol) and isopropyl alcohol (isopropanol). Figure 10.1 illustrates the structure of these widely used alcohols.

Ethanol, the most common form, is the type of alcohol used in alcoholic beverages and is simply called “alcohol”. Alcohol is a clear, almost odorless chemical that is infinitely soluble in water. It is also a psychoactive drug. Alcohol is made from fruits, flowers and other plants, which combined with sugar and yeast ferment to form ethanol. Compared to most other psychoactive drugs,

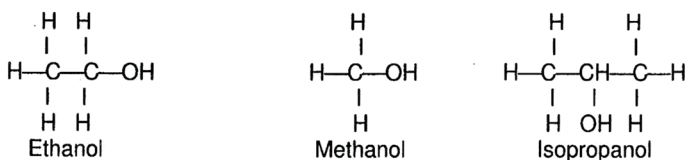


Figure 10.1 Structure of common alcohols

it is a simple molecule. Alcohol is made up of one oxygen, two carbon, and six hydrogen molecules and has the chemical structure and formula $\text{CH}_3\text{-CH}_2\text{-OH}$. As a drug, alcohol produces a dose-dependent biphasic effect on behavior and acts similarly to other central nervous system depressants.

Methyl alcohol or methanol is the type of alcohol used in cleaning agents, solvents, paint and dye. It is also frequently added to the gas tanks and radiators of vehicles in cold weather to prevent fluid from freezing.

Methanol has multiple other industrial and chemistry application and was used as part of the embalming process by ancient Egyptians. Methanol is highly toxic (retinal damage leads to blindness) and small amounts, as little as several ounces, can be lethal. Central nervous system toxicity includes signs similar to those produced by ethyl alcohol, including depression, lethargy, confusion, dizziness, coma or as a result of metabolism. Methanol is metabolized to formic acid, a cellular toxin by the enzyme alcohol dehydrogenase, the same enzyme that oxidizes ethanol in the liver.

The antidote for methanol poisoning is ethanol, because ethanol will be oxidized preferentially over methanol. This enables methanol to be excreted with minimal formation of formic acid. Unfortunately for some alcoholics entering a detoxification ward (detox) who have consumed methanol, a misdiagnosis of alcohol intoxication rather than methanol poisoning can be fatal. If you work in a detox ward, always determine if there is a history of drinking anything other than beverage alcohol.

Isopropyl alcohol or isopropanol is used in rubbing alcohol. This type of alcohol is used to cleanse the skin or disinfect objects and is found in various hair and skin products. Isopropyl alcohol is also highly toxic and can produce nausea, vomiting, headache, dizziness, confusion, poor coordination and coma. Small amounts, as little as several ounces, can cause permanent damage to the visual system or death. Isopropyl alcohol is sometimes consumed by alcoholics in place of ethanol. The same warnings given for methanol apply to isopropyl alcohol.

History of Alcohol Use

There is evidence that prehistoric humans made wine and its use is well documented in the Bible and in ancient Egyptian pictographs. The oldest known scientific record of wine making comes from the Henan province of China where scientists discovered brass wine jars sealed by corrosion. The 9,000-year-old wine was still fragrant! Alcohol has been used for thousands of years and continues to be popular. Currently, more than 70 percent of all high-school aged Americans have tried alcohol and 54 percent have drunk to the point of intoxication.

Social Drinking

The social use of alcohol now generally includes uses such as a cold beer after a ball game, a glass of wine with meals, or a glass of champagne when toasting newlyweds at a wedding reception. Greater consumption is often labeled abuse or misuse, when alcohol consumed causes danger to the drinker or to others affected by the drinker's behavior. Light, moderate, and heavy drinking can be defined by various methods and criteria. For example, the term "moderate drinking" has been defined by the US Department of Health and Human Services and the US Department of Agriculture as one drink for women and two drinks for men, per day. Current US dietary guidelines define high-risk drinking for men as more than four drinks per day (or more than 14 drinks per week) and for women more than three drinks per day (or more than seven per week). Binge drinking is now defined as the consumption of more than four or five drinks within two hours for women or men, respectively. These distinctions may not reflect safe or high-risk drinking depending on the density of drinking. For example, two drinks per day (for men) has very different risk consequences than 14 drinks consumed in one day, even though the total weekly consumption is the same.

Alcohol Use Disorders

The current Diagnostic and Statistical Manual of Mental Disorders (DSM-V) identifies two groups of substances-related disorders; those with substance-use disorders, (characterized by using a substance even though problems occur) and substance-induced disorders (intoxication, withdrawal or other

mental disorders caused by use). A more detailed discussion of DSM diagnostic criteria for substance use disorders (SUDs) and how current definitions differ from previous diagnostic criteria is discussed in Chapter 16.

In DSM-V, Substance Use Disorder: Severe describes users with multiple criteria that include withdrawal symptoms. Notwithstanding the re-emerging concept that addiction is a behavioral disorder (see Chapter 16 for discussion of this ongoing debate) the fact remains that all behavior has a neurophysiological basis and genetic influences that also affect risk for this SUD. While we hold that some people have a medical disease based on brain chemistry dysfunction, there is no magic bullet to treatment. Also, treatments restricted to pharmacotherapy are likely to be less effective in treating the behavioral complexities of use, misuse, craving and the multitude of behavioral components of problem drinking.

Alcohol use can lead to physical dependency and manifestation of withdrawal when drinking stops. The term alcoholic is now considered pejorative and is replaced by the term alcohol use disorder (AUD). However, because so much of what we know is based on previous research with “alcoholics” the term is sometimes more useful in understanding the diagnostic criteria for subjects at the time of the study.

Who Drinks?

The short answer is most people. In the US about 78 percent of people age 12 or older have consumed alcohol at some time in their life. Among older (18+) persons, about 85 percent have consumed alcohol at some point. A better indicator of who drinks regularly comes from surveys about alcohol use in the last 30 days. About 50 percent of men (age 12 and older) and 45 percent of women (age 12 and older) have consumed alcohol in the last month. Among adults about 52 percent have consumed alcohol in the last month. Generally, men report alcohol use slightly more than women.

Among problem drinkers, there are about three times as many biological males who meet criteria for alcohol use disorders as compared with biological females. The epidemiology of alcohol use disorders in persons who identify as a gender different from their genetic gender is not known at this time but this cohort will almost certainly be the focus of future research. It does appear that alcohol use disorders among women are increasing as more women are exposed to the stress of the workforce or the combined stress of

working both in and out of the home. Nevertheless, alcohol use disorders are still lower in women. This continued gender difference may be due to social factors, possibly a “protective” gene, or brain chemistry that is more resistant to alcohol. Whatever the case, male and females can get into trouble with any alcoholic beverage (beer, wine, or spirits) and there does appear to be a strong hereditary component of alcoholism. Studies on families, twins, and adopted children of alcoholics, and nonalcoholics over the past 20 years have shown clearly that about 60 percent of the contributing causes to alcoholism are hereditary. This “tendency to become alcoholic” is inherited and means that 40 percent of the causes of alcoholism are environmental (psychological or social). There are also probably subtypes of alcohol dependence, suggesting several different causes of the diseases known as alcoholism. Exciting new neurobiological, genetic, and psychosocial research is ongoing to further understand the complex causes and issues surrounding problem drinking of all types.

Administration, Absorption and Distribution

How Alcohol Gets into the Body

Before alcohol can exert any short- or long-term effect on the brain and behavior, it must enter the body where its fate is subject to physiology and the absorption, distribution, metabolism and elimination of the alcohol.

Absorption

In humans, the primary route of alcohol administration is by mouth (although intravenous alcohol injections and alcohol enemas have been reported!). When alcohol is swallowed it enters the stomach. The transit from the stomach into the small intestine is regulated by a ring-shaped muscular valve called the pyloric sphincter. Under laboratory conditions in which the pylorus has been clamped closed or ligated, about half the alcohol in the stomach will eventually be absorbed through the stomach wall and into the blood. However, under more natural drinking conditions, about 10 percent of orally ingested alcohol is absorbed through the stomach; the rest is absorbed through the upper intestine and into the circulation.

The concentration of alcohol in the blood is a function of many factors including (1) the amount consumed, (2) the rate at which alcohol enters the circulatory system from the gastrointestinal tract, (3) the diffusion and distribution of alcohol into blood and fluid compartments, (4) the rate at which alcohol is oxidized and eliminated and (5) the time course of drinking.

As alcohol and other stomach contents are digested, they pass from the stomach into the small intestine. Because alcohol is a weakly charged molecule, it passes easily through lipid membranes and is highly soluble in water. Alcohol moves through the duodenum or upper part of the small intestine into the capillary plexus, a network of tiny blood vessels surrounding the intestines. From there, alcohol enters the hepatic portal vein to the liver and continues to move from the liver to the heart, where it circulates to the brain and other parts of the body (see Figure 3.2).

Alcohol may enter the circulation through several routes including the pulmonary system, the skin, or by injection. Although the efficacy of some of these routes is questionable in humans, they are often used in animal models.

Factors Affecting Absorption

Beverage Characteristics

The speed at which alcohol can be absorbed, and the amount, may be affected by the concentration and type of alcoholic beverage. For example, older studies have found that in humans the absorption of alcohol is most rapid when administered in a 15 to 30 percent solution and less rapid when the concentration is below 10 percent. Beverages with low concentrations of alcohol, such as beer, are probably absorbed more slowly due to the effect of volume on gastric emptying time, or as Fick's Law would predict, the lower concentration gradient results in slower diffusion per unit area per unit time. Many studies examined beverage characteristics using low doses of alcohol. In laboratory studies, the entry of high concentrations of alcohol into the circulation may be delayed by gastric peristalsis and pylorospasm. This effect is probably reduced if the person regularly consumes highly concentrated alcohol. Results from older studies indicate that carbonated beverages such as champagne may also be absorbed faster than noncarbonated drinks but the clinical significance of this in drinking situations outside the laboratory is altered by other factors affecting absorption rate.

Beverage type may also influence the rate of absorption. For example, beer is absorbed more slowly than whiskey or brandy probably because of the larger fluid volume in a 12-ounce beer versus 1.5 ounces of distilled spirits, even though the total alcohol content is approximately the same. Interestingly, even if these beverages are diluted to the same ethanol concentration, differences in absorption rates between types of alcoholic beverages are still observed, perhaps due to differences in carbohydrates or congeners. However, once the alcohol passes out of the stomach and into the intestine, absorption into the circulation is rapid, complete, and not affected by the concentration of alcohol in either the stomach or the intestines. In other words, the stomach environment is the primary rate-limiting factor in alcohol's absorption, although genetic factors may also play some role.

When the rate of absorption exceeds the rate of elimination, blood alcohol concentration (BAC) rises. Therefore, the rate of alcohol absorption directly affects the maximum BAC. The faster the rate of alcohol absorption, the greater the area under the blood alcohol concentration curve (see Figure 10.2). Similarly, decreasing the rate of absorption decreases the area

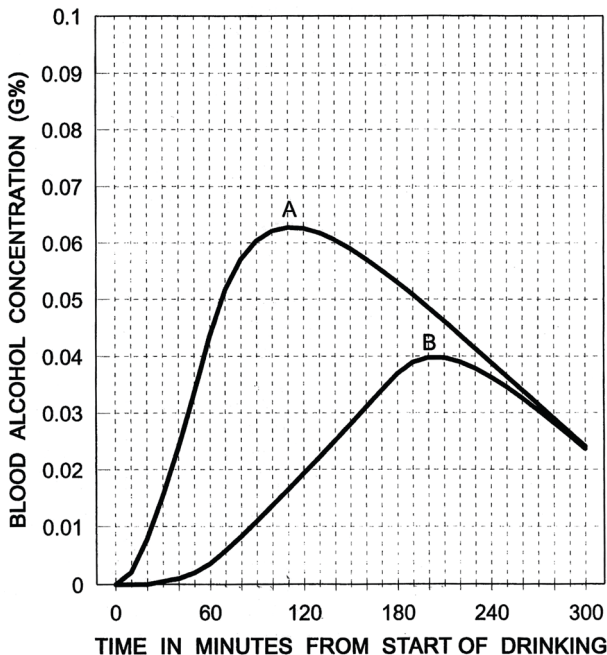


Figure 10.2 Different rates of drinking the same quantity of alcohol alter the maximum blood alcohol concentration

under the curve and peak concentration, and increases the time from the last drink to maximum concentration. Absorption is affected by many variables, but in the absence of any pathological condition, the two most critical factors are presence or absence of food and volume of beverage.

Food

The absorption of alcohol from the gastrointestinal tract into the blood supply is significantly influenced by the presence of food in the stomach. Alcohol is absorbed much more rapidly on an empty stomach than on a full one. The delay in absorption of alcohol from the gastrointestinal tract into the circulation is similar when food is consumed before, during or just after alcohol. The presence of food in the stomach not only impairs absorption but reduces gastric emptying time and consequently will result in lower BACs. Although earlier studies indicated that food type may also affect absorption (e.g., proteins and carbohydrates were more effective than fats in delaying ethanol absorption), it is difficult to accurately make pharmacokinetic predictions regarding the blood alcohol based upon different food types.

Volume

Gastric emptying is also directly related to the volume of the gastric contents. Stomach emptying is regulated in two ways: (1) the receptive capacity of the intestine (which regulates outflow from the stomach based upon the volume and pressure within the intestine); and (2) volume of contents in the stomach.

The rate of gastric emptying is a balance between the force and frequency of gastric peristalsis (muscular movement in the gastrointestinal system) and the resistance of the pylorus (the muscular valve that regulates stomach emptying). Gastric emptying is directly related to the volume of fluid in the stomach. The distention of the stomach activates afferent vagus nerve impulses from gastric stretch receptors. The activation of these receptors results in a vagal nerve impulse that increases both gastric peristalsis (the alternating contraction and relaxation of muscles) and gastric emptying. Working in concert with the stomach to control gastric emptying, the duodenum decreases gastric peristalsis and limits the volume of matter that enters the intestine to one that can be efficiently processed. In this way, as the volume

of fluid in the stomach increases, so does the volume that passes into the intestines and quickly into the circulation.

Large volumes of fluid ingested over a short period of time will result in a rapid increase in BAC. However, the large volumes will take longer to be absorbed from the gastrointestinal system to the blood. Sophisticated algorithms to account for absorption are discussed in Chapter 18.

Once drinking stops, the volume of alcohol in the stomach decreases and the slope of the ascending blood alcohol curve also decreases until such time as the amount of alcohol being absorbed is equal to the rate of elimination. Then the maximum BAC is obtained. Thus, an exponential calculation, proportional to the amount of alcohol consumed, provides a reasonable scientific estimate of alcohol absorption under a range of drinking conditions. Differences in beverage volume, volume of distribution, alcohol concentration, the presence or absence of food and rate of elimination, coupled with drinking time and amount of alcohol consumed, determine the ultimate shape of the blood alcohol curve.

Alcohol Absorption After Drinking Stops

Alcohol absorption and peak BAC are important parameters in calculating the blood alcohol curve over time. In some single-dose studies, remarkable variability in time to peak BAC has been reported. This variation is a function of many factors, including drinking density (amount of alcohol per hour). In controlled laboratory studies the between-subject variation for time to maximum BAC following the same dose is quite low (e.g., less than 15 minutes). Under most drinking scenarios, alcohol absorption exceeds elimination for about 30 to 90 minutes after the last drink.

Distribution

Regardless of the route of administration, once ethanol enters the circulation, it is distributed throughout the water compartments of the body. Tissues with the greatest blood supply and capillaries (small blood vessels) receive alcohol more rapidly than tissues with fewer blood vessels. For example, it may take many hours for alcohol to equilibrate in bone, whereas brain, lung, kidney and liver tissues equilibrate very rapidly. Since alcohol is infinitely soluble in

water, at equilibrium, it is distributed equally throughout the watery portions of the body.

Factors Affecting Distribution

Gender Differences

Biological gender can affect the bioavailability of alcohol through gastric metabolism (as previously discussed) or through differences in the volume of distribution. On average, men have more muscle mass per pound of body weight than women. Also, on average, women have more body fat per pound of body weight. Since muscle cells have more water than fat cells, men generally have more total body water than women.

Age and height also influence the total body water. Differences in body water are important in calculating BACs or total alcohol consumed because the greater the total body water, the greater the alcohol dilution.

During the first third of the 20th century, a Swedish physiologist, E. M. Widmark, studied the interrelationship between the amount of ethanol consumed, body weight, elimination rate and the BAC. Part of this early work including estimates of body water. Widmark estimated the total body water, which he called the *Rho* factor, to be .68 for men and .58 for women. These values are the average percentages of total body weight represented by water. Since then, Widmark's equation has been modified to take into account more recent technological advances in the estimation of total body water. The most accurate estimates of total body water incorporate age, weight, height, and gender. The sophisticated algorithms to derive total body water based upon all known factors are given in Chapters 3 and 18.

Metabolism and Elimination

Some alcohol is metabolized in the stomach and elimination begins before absorption from the gastrointestinal tract is complete. In men, some alcohol is oxidized in the stomach by the enzyme gastric alcohol dehydrogenase (GADH). Inhibition of GADH by histamine antagonists such as Tagamet can elevate predicted BACs by as much as 10 to 20 percent and may explain differences in the bioavailability of alcohol between biological men and

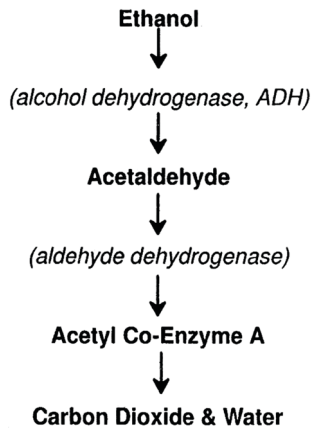


Figure 10.3 Oxidative metabolism of ethanol

women. More recent studies have questioned whether Tagamet, Cimetidine and similar stomach acid blockers significantly affect BACs when higher doses of alcohol are applied.

The majority of alcohol is metabolized in the liver by the enzyme alcohol dehydrogenase (ADH), which transforms alcohol to its primary metabolite, acetaldehyde. Acetaldehyde is quite toxic and is quickly transformed by another enzyme, aldehyde dehydrogenase, to acetyl-coenzyme A, which is eventually broken down to carbon dioxide and water and excreted (see Figure 10.3).

Widmark was the first to accurately describe the rate of alcohol elimination in humans and referred to this using the Greek letter beta (β). Widmark reported beta to be about 15 mg/dL/hr (.015 percent/hr). Subsequent studies reported a wide possible range of elimination rates, probably due to poor experimental design, poor subject screening and other factors. More recent studies using better analytical techniques have confirmed Widmark's original computation and have suggested that, except in some clinical populations, the rate of elimination is very centrally weighted at approximately .015 percent/hr. For example, in one study in the postabsorptive (after alcohol) state, BACs decreased at a rate of 14.94 mg/dL/hr (± 0.39 s.e.m.). Since the range of elimination from this data set was unusually large (6–28 mg/dL/hr), and the variance so small, these results indicate a normal distribution but one with a very central tendency. Very low rates of elimination are very rare and may be due to unaccounted for continued absorption of alcohol or other factors.

Most drinkers eliminate alcohol at .01–.02 percent/hr but a small segment of more tolerant drinkers eliminate alcohol at even higher rates up to about .025 percent/hr (or occasionally higher in instances with exceptional metabolic tolerance).

More recent studies have indicated that the rate of elimination is not constant. At very low BACs, the elimination of alcohol from the blood changes as a function of concentration (something termed first-order kinetics). When the concentration of alcohol falls below about .02 percent, the rate of elimination then decreases and the BAC profile looks like a curved line or “hockey stick”. While often discussed in the alcohol literature, this effect has little application to actual drinking and the change in elimination while observed in the laboratory, has little clinical or forensic application.

Less-Known Routes of Elimination

Approximately 90 percent of all alcohol is metabolized from the body through breakdown by the liver enzyme alcohol dehydrogenase. Small amounts of unchanged alcohol are eliminated from the body through sweat, urine and expired air. These can be measured in alcohol sweat patch tests, urinalyses and through breath testing. However, only measurement in breath can be carried out in a meaningful way.

What is a BAC?

Once alcohol has entered the body and the general circulation, the blood alcohol concentration increases. The BAC is the concentration of alcohol by weight in a volume of blood, almost always 100 milliliters (in the United States). The BAC is usually expressed in grams or milligrams (mg) of pure ethanol per 100 milliliters (mL) of whole blood or serum. The following BAC nomenclatures are identical:

$$\begin{aligned} .08\% &= .08 \text{ grams per } 100 \text{ mL of blood } (\%) = \\ 80 \text{ mg/dL} &= 80 \text{ mg } (\%) \\ \text{where dL} &= \text{deciliter, or } 100 \text{ mL} \end{aligned}$$

Keep in mind that while the BAC increases (with drinking and absorption) it is also being metabolized and eliminated. If more alcohol goes into the

blood than is removed by metabolism and elimination, the BAC increases and visa-versa.

Detection and Measurement of Alcohol

Alcohol use may also be detected through biobehavioral testing, toxicology tests and biochemical markers of long-term use and potential vulnerability for alcohol use disorders. These are discussed further in Chapter 17).

Qualitative detection of alcohol can be made through the skin with the use of transdermal patches and in urine.

Quantitative measurement of alcohol can be made in breath, blood, saliva and in postmortem samples (blood, vitreous humor, brain, bile, liver, gastric contents, blood clots). Quantitative analyses of alcohol in postmortem tissues (e.g., liver, brain, bile, gastric fluids) are often performed as part of an autopsy but do not directly relate to blood, serum or breath alcohol concentrations.

Detecting and measuring alcohol can be simple, easy or more complex requiring analytical instruments. The absolute simplest way to detect alcohol use is the odor of alcohol on the breath (AOB) by casual observation. Depending on location and proximity to the person, this may not be easy. However, absent medical conditions that may mimic alcohol-like odors such as diabetic ketoacidosis, the detection of AOB is a useful indicator of use. It is not however a measurement of alcohol intoxication. While there is a threshold above or below which AOB is or is not present, the strength of AOB is unrelated to any specific BAC.

Measuring alcohol in saliva is relatively easy and more specific than AOB and it can be quantitative. In this method, alcohol in saliva reacts with alcohol sensitive saliva strips that change color in proportion to the concentration of alcohol. This method is useful for quick compliance testing or other clinical applications. A more common technique for measuring alcohol is through the breath. This is the method used by most police departments because of the rapidity with which alcohol can be measured and because breath can be captured with minimal training, embarrassment and no pain. Breath testing is also used by clinicians in hospitals and treatment centers and alcohol researchers.

The most sophisticated and accurate method is to measure alcohol directly in blood. This can be accomplished with various approved breath alcohol testing devices or gas chromatography, the analytical standard for accurate and

precise alcohol testing. This is the method used by most forensic or research labs. Alcohol can also be reliably measured in serum (the watery portion of blood). This is the method used by most hospital. When alcohol is measured in serum, the concentration is higher than blood because of the differences in water content between whole blood and serum (see Chapter 18).

Calculating the BAC

The calculation of BAC is made by dividing the amount of ethanol consumed into the available body water. Body water is primarily a function of weight and gender, as described earlier. Using the total body water (TBW) algorithm (Chapter 3 and Chapter 18), the BAC in a man or woman can be calculated given certain facts or assumptions, including the amount of alcohol consumed and the elapsed time from the onset of drinking to the time of measurement. A relatively simple method is described below. See Chapter 18 for additional and more specific alcohol pharmacokinetic calculations.

Equation 10.1: General algorithm for calculating BAC

$$\text{BAC} = g / \Sigma_{\text{vd}} \times \text{BLH}_2\text{O} - [(\beta_{1-n} \times (ts + tp))]$$

Where:

BAC = Blood alcohol concentration

g = grams of alcohol

Σ_{vd} = Total body water

BLH_2O = Blood Water Coefficient

β_{1-n} = range of alcohol elimination rates (1-n)

ts = time from start of drinking

tp = range of absorption time from last drink to estimated peak BAC (usually 30–90 minutes)

Dividing the total grams of ethanol by the total body water in kilograms, multiplying the obtained quotient by the percentage of water in blood coefficient and subtracting the total amount of ethanol oxidized at a constant rate (b) from the time of the first drink (t) to time points corresponding with the maximum post-drinking absorption peak will produce reliable estimates of blood alcohol. Various slide rule devices and computer software programs have been developed to facilitate such calculations. Algebraic variations can

be used to answer more specific questions about alcohol that might involve forensic matters (see Chapter 18).

Neuropharmacology of Intoxication

Alcohol affects virtually every organ system in the body and alters the activity of most major neurochemicals. This explains, in part, the wide range of biobehavioral effects produced by its ingestion. Of particular interest is alcohol's effect on the GABA system. As we learned in Chapter 7, benzodiazepines, a class of anxiolytics (anxiety reducers) that has behavioral effects similar to alcohol, also exert their sedative effects through the GABA system. The combined number synapses in the brain that respond to GABA, the most abundant excitatory neurotransmitter in the brain and glutamate, the major excitatory neurotransmitter exceeds those used by all other neurotransmitters combined. In other words, GABA and glutamate are present throughout most of the brain.

No Magic Bullet for Sobriety

Alcohol's action is, in part, related to GABA-linked changes in chloride ions flux. Like benzodiazepines, alcohol enhances the inhibitory GABA system at the GABA_A receptor subunit. Evidence that alcohol exerts intoxication through the enhancement of the GABA system is based, in part, on evidence that when chloride ion flow into GABA neurons is blocked with an experimental drug, an imidazodiazepine called RO-15-4513, many of the behavioral effects of alcohol intoxication are completely reversed in experimental animals. What makes this effect so intriguing is that there is no change in BAC. In other words, the animal is still pharmacologically intoxicated (at high levels) but there is no impairment on behavioral tests that are normally sensitive to alcohol intoxication. RO-15-4513 is not available for human use because it has harmful effects on the liver.

It is believed that the sedative effects of alcohol are a combination of enhanced GABA transmission and decrease in glutamate attenuation. Alcohol also increases serotonin activity and dopamine release in brain reward pathways. Another subunit of the cell, is n-methyl-d-aspartate (n-NMDA). NMDA which is a receptor for glutamate, is highly sensitive to low doses of

alcohol in the laboratory. Alcohol inhibits nNMDA but over time, the decrease in NMDA sensitivity to alcohol inhibition which may explain the development of some forms of tolerance. However, this effect is not seen in all brain areas. Scientists continue to focus on the interaction between alcohol use, intoxication and alcohol use disorders (various) and either different neurotransmitter receptor systems for dopamine, acetylcholine (nicotinic), NMDA, GABA, serotonin, cannabinoid and the endorphin-opioid system.

To summarize the neuropharmacology of acute and chronic alcohol is complex, dose-dependent, varies with acute or chronic use and involves many different brain areas mediating behavior and the changes in excitation, inhibition and release of excitatory or inhibitory neurotransmitters on various receptors and receptor subtypes appears to be more complicated than for other drugs that act, largely on specific receptors. In the future and as our knowledge increases, we may require the power of artificial intelligence (AI) to detect patterns and predictive algorithms to help understand the dynamic interplay between the brain and behavior.

Biobehavioral Effects of Alcohol Intoxication

Alcohol is generally classified as a central nervous system depressant. It produces a dose-dependent decrease in cognitive and motor functioning. As BACs rise, the signs and symptoms of impairment increase in number and intensity.

The behavioral signs associated with alcohol intoxication may include decreased inhibitions (people say or do things they would not normally do when sober), psychomotor impairment (loss of fine and gross motor control such as hand-eye coordination, ability to stand, walk, and/or balance, reaction time, changes in speech articulation, richness, coherence and volubility), and impaired cognitive abilities (e.g., problem solving, memory, risk assessment) and good judgment are diminished. These signs of intoxication fall into three basic categories: **Decreased Inhibitions**, **Psychomotor** and **Cognitive impairment** and can be remembered using the mnemonic, DIP-C.

In most drinkers, as the BAC increases toward 80 mg/dL (.08 percent), it becomes increasingly difficult to perform various complex psychomotor tests, including tasks such as driving. It is for this reason that the legal definition for intoxicated driving (in the US) is set at .08 percent for non-commercial operators. However, it is difficult, in the absence of specific testing, to reliably

Table 10.1 Biobehavioral Effects of Alcohol Intoxication®

BAC (grams %)	ASSOCIATED EFFECTS
.02–.04%	Increased relative risk for motor vehicle crash starts for some motorists, particularly young drivers Impairment not detectable without special lab tests Exceeds zero tolerance laws for underage drinkers Subjective warm, mellow or relaxing feeling, enhanced sociability
.04%	Start of some cognitive and psychomotor impairment not likely detected by casual observation. Federal definition for DWI for commercial vehicle operators
.05%	Increased risk for pedestrian fall-down and other injuries Driving impaired by most legal standards
.08%	National legal definition for DWI/DUI Virtually all drivers too intoxicated to drive safely Odor of alcoholic beverage on breath in most drinkers (varies)
.15%	Reliable signs of visible intoxication begin to appear in >50% of drinkers and increases significantly with higher BACs Most drinkers display classic signs of <u>visible intoxication</u> (e.g., one or more signs of: decreased inhibitions, impaired psychomotor and diminished cognitive skills) without the use of police field or laboratory tests
.20%–.25%	Severely impaired sensory (e.g., visual, tactile) and motor (e.g., standing, walking, balancing) and cognitive processing
.30%	All but exceptionally tolerant drinkers are stuporous or unconscious
.35%	Low range of surgical anesthesia
.40%	Estimated lethal level for significant portion of the population

The biobehavioral effects described are cumulative and dose-dependent. Signs present at lower blood alcohol levels increase in number or intensity at higher alcohol concentrations. Modified from Alcohol: The socially acceptable addictive drug. In: *Drugs, The Brain, and Behavior: The Pharmacology of Drug Use Disorders* © 2013.

observe and identify symptoms of alcohol intoxication until BACs reach 150 mg/dL (.15 percent). At that level or more, the majority of people will show signs or symptoms of impairment due to alcohol intoxication, even in the absence of specific testing.

Table 10.2 Major Categories and Common Signs of Alcohol Intoxication*

Decreased Inhibitions

1. Doing things that would normally not be done when sober
 2. Saying things that would normally not be said when sober
 3. Boisterous
 4. Argumentative
 5. Confrontational
 6. Obnoxious
 7. Annoying to others (e.g., strangers)
 8. Hanging on to people or otherwise intruding on their personal space including excessive physical contact
 9. Loud comments about other people in the vicinity
 10. Animated or exaggerated speech or actions
 11. Rapid drinking
 12. Acting silly or “cutesy”
 13. Complaints about drink strength or service
 14. Bravado
-

Psychomotor Impairment

15. Slurred, mumbled or incoherent speech
 16. Slow speech
 17. Swaying while sitting, standing, or walking
 18. Staggering, stumbling, holding onto objects for balance
 19. Difficulty reaching for and picking up money, food, drinks, etc.
 20. Inability to maintain eye contact (lack of focus or wandering gaze)
 21. Head down or asleep
 22. Falling off stools, chairs, etc.
 23. Bumping into objects or people while walking
 24. Leaning for support while standing, walking or sitting
 25. Exaggerated hand or arm gestures
 26. Spilling food or drinks, dropping objects
 27. Loss of balance while standing, walking, negotiating turns
-

Cognitive Impairment

28. Loss of concentration or train of thought, confused
 29. Delayed response to questions
 30. Illogical comments or answers to questions, non-sequiturs
 31. Impaired short or long-term memory
-

Table 10.2 Cont.**Cognitive Impairment**

-
32. Lighting more than one cigarette at a time or not smoking a lit one
 33. Lighting the wrong end of a cigarette
 34. Taking another person's food, drink or cigarette
 35. Excessively quiet, sullen
 36. Denial of impaired driving ability
 37. Consumption of large amounts of alcohol or rapid drinking
 38. Trouble counting money or with basic math
 39. Difficulty following instructions or directions
-

*Not inclusive of every possible sign of intoxication.

Modified from: Brick, J. and Erickson, C. (2009). *Alcoholism: Clinical and Experimental Research*, 33(9), pp. 1489–1507.

Driving and Other Complex Divided Attention Tasks

One of the most pronounced effects of alcohol is on divided attention tasks (see Figure 10.4). For example, operating a motor vehicle requires the driver to attend to and remember many tasks. Alcohol intoxication may interfere with the ability to remember to wear a seat belt, turn on driving lights and/or directional signals, attend simultaneously to other vehicles, pedestrians, traffic control devices, road markings, hazards, or signs, and to control lane position, speed, make estimates of time and distance, etc. Over the course of many decades, multiple authorities agree that even at low BACs below the legal definition of intoxication for DWI/DUI, impairment is significant and motor vehicle operation is impaired.

For example, sensory, motor and intellectual faculties,

... have been studied extensively through laboratory, closed-course and on-road driving and epidemiological studies. The scientific literature provides a high degree of confidence to support the conclusion that a BAC of .05% impairs faculties required in the operation of a motor vehicle.

Martin, et al. (2013). A review of alcohol-impaired driving: The role of blood alcohol concentration and complexity of the driving task. *Journal of Forensic Science*, 58(5): 1238–1250

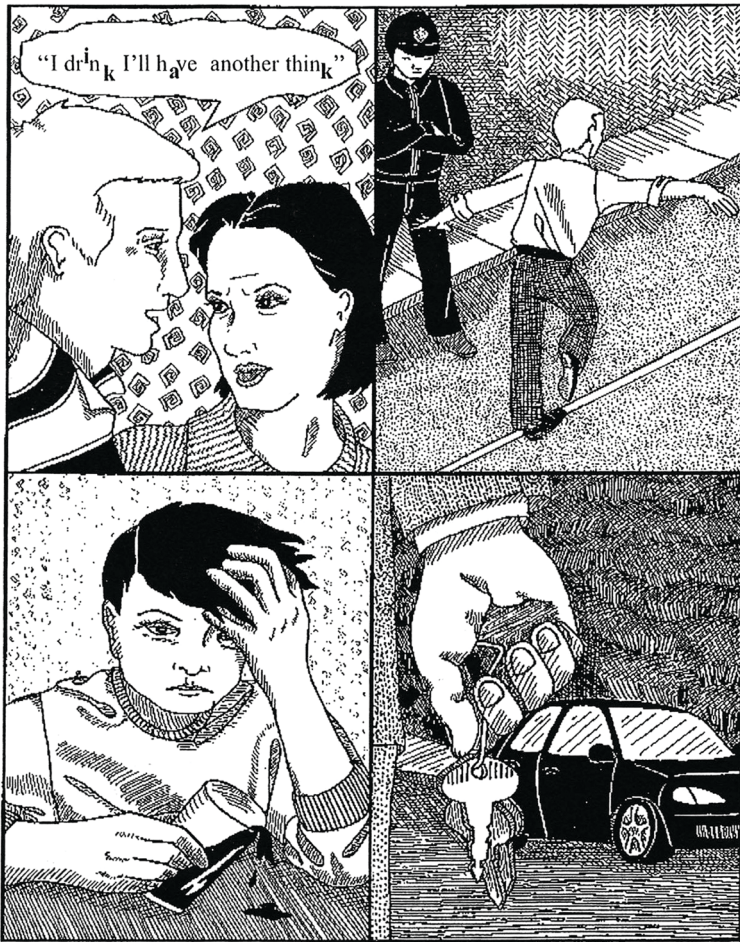


Figure 10.4 Alcohol impairs many domains of cognitive functioning

Data from numerous studies demonstrate that divided attention deficits occur in the 0.02 to 0.10 percent BAC¹ range. In a more recent study...[it] showed divided attention impairment at lower BACs (0.015%, 0.03, 0.045 and 0.06 percent).

Alcohol World. National Institute on Alcohol Abuse and Alcoholism. US Department of Health and Human Services (p. 14)

...alcohol increases fatal crash risk more for younger drivers than for older ones, and moderate BACs profoundly enhance crash risk among drivers aged 16 years through 20...

Special Report to the US Congress on Alcohol and Health. US
Department of Health and Human Services, National Institute on
Alcohol Abuse and Alcoholism (p. 240)

and in a comprehensive review it was concluded that,

"...even at BACs of 0.05%, the probability of being involved in an accident has increased 100%, and for young drivers this probability has increased several hundred percent" (p. 1). The report goes on to conclude, Areas such as oculomotor function and divided attention performance demonstrate that impairment can occur at BACs as low as 0.02%. It is clear, moreover, that BACs of 0.05% or more impair nearly all of the important components of driver performance. In assessing the minimum BACs required to produce performance decrements relevant to driving, it can be noted that for most of the performance areas discussed here impairment has been reported at BACs between 0.01 and 0.02%

US Department of Transportation
National Highway Traffic Safety Administration
DOT HS 807 280 (1988; p. 67)

... the National Safety Council Committee on Alcohol and Drugs recommended that the presumption that an individual is not impaired when the [BAC] is below 0.05% be stricken from DWI legislation, since recent evidence shows that the performance of a substantial number of individuals is impaired at [BACs] below 0.05.

Surgeon General's Workshop on Drunk Driving. US
Department of Health and Human Services, Office of the
Surgeon General (noted p. 139)

In a comprehensive review of the evidence,

From a scientific point of view, there appears no lower BAC below which impairment cannot be said to exist.

Moskowitz and Robinson, et al. (1988).
Effects of low doses of alcohol on driving-related skills:
US DOT NHTSA Report DOT HS 807 280

At high BACs the performance of these skills is further hampered by analgesia and impaired feedback from tactile (touch) receptors in the skin. (This type of feedback is called proprioception).

Intoxicated pedestrians are also affected by alcohol. Like motorists, pedestrians must divide their attention among many different tasks. When sober, most of these tasks are performed without difficulty or conscious effort but not so when intoxicated. Alcohol intoxication may interfere with the ability to walk, in which it is necessary to: lift the foot, flex the foot, step forward, rotate the hip, redistribute the weight to the load bearing leg and repeat this sequence, while also allowing for changes in the road surface, elevation, etc. Alcohol intoxication also interferes with the ability to balance, attend simultaneously to traffic control devices, signs, road markings, road or walkway hazards, or to monitor traffic and other vehicles, make estimations of time, distance and speed, etc.

When an intoxicated individual needs to simultaneously attend to the many components involved in walking as well as to highway, roadway, or structural challenges that require divided attention, that person is at increased risk for an accident. For these reasons, at a BAC of more than 80 mg/dL (the current legal definition for intoxicated driving in the US), most individuals will be at significant risk for an accident due to the intoxicating effects of alcohol.

People rarely look visibly intoxicated at BACs that produce impairment in complex divided attention tasks, such as driving. Most drinkers will not appear visibly intoxicated (impaired) at BACs of .08 percent, unless they are given specific tests. The reality is that virtually all drinkers are at increased risk (Table 10.3) for an accident at BACs that do not necessarily produce visible intoxication. Many foreign countries use .05 percent as the legal limit and in the US, .04 percent is the legal definition for intoxication in commercial vehicle operators. The scientific evidence (although incomplete) suggests that a lower DWI limit (e.g., less than or equal to .08 percent) may be justified. Finally, in multiple domains of everyday activities, including driving, bicycling, swimming/boating, and other common activities, alcohol intoxication increases the risk for accidental injuries.

Tolerance and Dependence

Alcohol tolerance refers to biobehavioral changes that occur in response to exposure to a drug. In this chapter, the focus is on alcohol, but tolerance to

Table 10.3 Relative Injury Risk: Effect of Mode, Age, Gender and BAC

Type of injury	Fatal motor vehicle				Fatal boating	Fatal or serious bicycle	Pedestrian fall-down injury	Biobehavioral effects of alcohol and related legal definitions of intoxication
BAC (%)	Age 16–20 ♀	Age 16–20 ♂	Age 21–34 ♀ and ♂	Age 35+ ♀ and ♂	ALL [including swimmers]	Effect of age/gender unknown	Effect of age/gender unknown	
Relative Risk								
.02	1.8	2.4	1.8	1.7	1.7			.02% Zero Tolerance
.03	2.5	3.7	2.4	2.3	2.2		-	(<21)
.04	3.3	5.8	3.2	3.0	2.9	6x		.04% National DWI
.05	4.5	9.0	4.3	3.9	3.7	(.02–.08%)		Commercial Operators
.06	6	14	6	5	-		3x	.08% National DWI
.07	8	22	8	7	-		(.05–.10%)	Psychophysical Impairment (SFSTs)
.08	11	34	10	9	7.1			
.09	15	53	14	11	-			
.10	20	82	18	15	10.4			
.11	27	127	24	20	-	>20x	10x	
.12	37	196	33	26	-	(≥.08%)	(.10–.15%)	
.13	49	305	43	33	-			
.14	67	473	58	44	-			
.15	90	735	78	57	23.0			
.16	122	1141	104	75	-		>60x (>.16%)	

(continued)

Table 10.3 Cont.

Type of injury	Fatal motor vehicle				Fatal boating	Fatal or serious bicycle	Pedestrian fall-down injury	Biobehavioral effects of alcohol and related legal definitions of intoxication
BAC (%)	Age 16–20 ♀	Age 16–20 ♂	Age 21–34 ♀ and ♂	Age 35+ ♀ and ♂	ALL [including swimmers]	Effect of age/gender unknown	Effect of age/gender unknown	
Relative Risk								
.17	164	1772	138	99	-			.15%
.18	221	2752	185	129	-			Visible Intoxication
.19	299	4273	247	169	-			(>50%)
.20	403	6634	330	221	39.4			Severe Sensory
.22*	735*	15995*	590*	380*	-			Motor Impairment
.24	1339	38561	1054	652	-			
.26	2440	92967	1881	1119	-			
.28	4447	224134	3361	1920	-			Stupor
.30	8103	540365	6003	3295	-			Unconsciousness
>.40%	-	-	-	-	-			LD:50 (Est.)

Adapted and modified from: Brick, J. (2015). *Alcohol intoxication and injuries: Wiley encyclopedia of forensic science*, A. Jamieson and A. Moenssens, (eds.), John Wiley and Sons, Ltd. Publishing Company. fsa 1131.

Relative risk (RR) for a fatal single car crash derived from stepwise logistic regression coefficients rounded to nearest tenth or whole number. For women age 16–20, a coefficient of 0.03 (range 0.044–0.014) was used (Zador et al., 2000a,b). Bicycle risk derived from Li et al. (2001); Pedestrian risk derived from Hokanen et al. (1983). Boating risk derived from Smith et al. (2001). Further details available on request or see text. Also included are biobehavioral descriptors. Values for BACs above * are included only for comparative purposes.

other drugs is similar. Different types of tolerance, both pharmacological and non-pharmacological, develop as alcohol alters the physiological actions of cells mediating physiology and behavior. As the brain adapts to the presence of alcohol, greater amounts of alcohol are required to achieve the original effect. This is the start of the tolerance cycle. A tolerant drinker requires more alcohol than a non-tolerant drinker in order to obtain the same effect although tolerances do not develop at the same rate for all domains of functioning.

Chronic heavy drinkers may become exceptionally tolerant to the intoxicating effects of alcohol so that an amount of alcohol that would cause overt intoxication in a social drinker may have little or no such effect in a chronic heavy drinker. Such individuals must often consume significant amounts of alcohol before they show visible signs of intoxication. Nevertheless, such drinkers are intoxicated, impaired and at increased risk for a variety of injuries due to their intoxication.

Medical Consequences of Alcohol

Accidental Injuries

Alcohol intoxication produces direct medical consequences as a result of motor vehicle, fall down, water-sport, burn injuries and pedestrian fall-downs. The consequences of intoxication also affect injury outcome. Contrary to popular misconception, drunk drivers, for example, are not protected by their intoxication. In actuality, intoxicated patients with head injuries are more likely to die from, or die sooner from head injuries as compared with being sober. Age, gender and amount of drinking over time are all factors that increase risk for fractures due to direct or indirect alcohol-induced changes in bone fragility and hormonal status (e.g., pre- or postmenopausal).

Alcohol intoxication may also affect injury outcome. This may be a factor in determining cause of death issues. For example, studies of hospitalized trauma victims with BACs of about .15 percent were significantly less likely to die from injuries than victims who were sober. Similarly, injury severity and mortality were inversely related to BAC. However, other studies have reported just the opposite. For example, motorcycle drivers with head injuries are about twice as likely to die from those injuries if they are intoxicated, and intoxicated drivers (BACs greater than .10 percent) are twice as likely to suffer serious injury or death compared to sober drivers, even when injury-related

variables such as vehicle size, speed, driver age, vehicle damage, and seatbelt use were taken into account. The interrelationship between intoxication and risk for an injury is clear. Less clear but of particular interest is the interrelationship between intoxication and injury outcome. More recent studies suggest that alcohol increases the severity of hemorrhagic shock and acidosis and probably decreases the likelihood of a favorable outcome.

Not all of the effects of alcohol occur rapidly, as in the cases of motor vehicle crashes, pedestrian falls or suicide.

Suicide

Alcohol use and suicide are prevalent world-wide and the link between alcohol use and suicide has been known since the mid-1960. Suicide is difficult to predict. Yet, when acute or chronic alcohol intoxication-induced, impulsiveness, impaired judgment and cognitive skills, enhanced aggression including self-aggression are coupled with psychosocial factors, the risk for suicide is elevated. Behavioral influences include a wide range of complex social factors including economic loss, familial, personal crisis (e.g., death of a spouse or loved one, job or housing loss) are red flags for possible risk but particularly so when AUD is present.

Pre-existing psychiatric disorders (alcohol dependence with major depression) are frequently reported in subjects who commit suicide. It is difficult to determine which specific factors or combination of factors contribute to suicide because the person is dead. Social environmental factors, lack of coping skills and despair are often present in non-alcohol related suicides as are genetic influences including susceptibility to stress and mood disorders. Predictably, co-morbid psychiatric disorders are common in patients with AUDs who attempt or complete suicide attempts. Depression and or alcoholism are co-morbid in about 85 percent of completed suicides. However, alcohol use is not a required condition of suicide but it is certainly a contributing factor and patients with AUD and depression require a higher level of vigilance and treatment.

Overdose

Death is of course a serious medical consequence of an accidental injury or overdose. As a central nervous system depressant, alcohol overdose can

suppress vital life sustaining areas of the brain involved in respiration and heart rate. All but the most tolerant of drinkers will lose the ability to maintain consciousness at BACs above .30 percent (300 mg/dL), exposing them to environmental or other dangers. Fatal overdose due to the depressant effects of alcohol are often reported at BACs above .40 to .50 percent (400 to 500 mg/dL) and it is in this range that the lethal dose for about half the population is estimated, although it is ethically impossible to test the LD:50 in humans. Even so, there are some individuals with such tolerance that they have survived BACs at more than twice these levels (i.e., greater than 1 percent or 1,000 mg/dL).

Organ and Tissue Damage

Some medical consequences of alcohol are more insidious, taking years to unfold before any significant medical consequence is detected. Chronic heavy drinking can produce cardiovascular diseases (e.g., heart disease, hypotension, increased risk for stroke), brain damage (cerebellum degeneration, enlarged ventricles), pancreatitis, peripheral nerve damage (e.g., neuropathies, paresthesias), neurological damage (cognitive and memory impairment), skin disorders, motor disorders (gait), changes in bone growth recycling that leads to osteoporosis and increased risk for fractures and certain forms of cancer.

Cancer

Long-term alcohol use is also linked with increased incidence of various cancers, particularly in tissues that have direct first contact with alcohol. For example, some research indicates as few as three drinks a day drastically increase the risk of esophageal cancers. Alcohol consumption is also associated with increases in head, neck and liver cancers. Increased risk for breast cancer has been reported, but the increase is relatively small. The risk between alcohol use and other forms of cancer is not clearly established.

Heart Disease

Cardiovascular disease is the leading cause of death among Americans, followed by cancer and stroke and it has been known for nearly 100 years that heavy drinking decreases longevity and is inversely associated with heart damage.

Alcoholic Cardiomyopathy (deterioration of heart tissue) is one of the most serious consequences of chronic heavy drinking. As cardiac cells deteriorate, their ability to contract decreases. This leads to enlargement of the heart (cardiac hypertrophy) but this compensatory response is short lived. Alcoholic cardiomyopathy is the most common cause of non-ischemic cardiomyopathy in Western societies and is a major source of heart failure and death.

Coronary heart disease occurs across a wide range of drinking patterns, don't rush to that next drink. The effect is limited to "light to moderate" drinking ranging from one to three drinks per week or no more than one to two drinks per day. However, not all studies have observed this so-called protective effect of alcohol. There is evidence that moderate drinking in a controlled setting (e.g., not in an automobile) is potentially beneficial in reducing heart attacks but critics have pointed out that "sick abstainers" may account for the paradoxical beneficial effects of low consumption. There is little doubt that heavy drinking has the opposite effect (see Medical Consequences, this chapter). Nevertheless, authoritative guidelines recommend against starting drinking or drinking more often to achieve any potential health benefits of alcohol. Moreover, coronary heart disease mortality is greater with higher consumption over time and offset by increased risk of death from other types of heart disease, including hypertension (discussed below) cancer, liver cirrhosis and trauma.

Hypertension

Moderate alcohol consumption (about one to three drinks per day) is associated with a slight reduction in blood pressure and may protect against age-related development of hypertension. As with other potential benefits of moderate drinking, the significance of these findings may be offset by an increased risk of death from causes unrelated to cardiovascular disease (e.g., accidental injuries, liver disease, etc.). Heavy alcohol consumption may also alter peripheral regulation of blood pressure by affecting smooth muscle cells in the walls of blood vessels and increase blood pressure leading to other risks, such as cerebrovascular events (e.g., stroke).

Stroke

There are two common forms of stroke: ischemic (when a blood vessel in the brain is blocked) and hemorrhagic stroke (when a blood vessel in the brain

ruptures). Alcohol-related hypertension, or high blood pressure, may increase the risk of both forms of stroke.

A review of the relationship between alcohol consumption and stroke risk revealed no differences in the risk patterns for ischemic or hemorrhagic stroke. Low doses of alcohol may have some beneficial effects, possibly due to the ability of alcohol to lessen damage to blood vessels due to lipid deposits and to reduce blood clotting. Heavy drinking appears to increase the risk of hypertension and, although the evidence is not entirely consistent, may also increase the risk of stroke. It remains uncertain whether lower levels of alcohol can help prevent ischemic stroke.

Liver Disease

After alcohol leaves the gastrointestinal tract, it travels via the hepatic portal vein from the small intestines to the liver, the largest organ in the body and the primary site of alcohol metabolism. Epidemiological data clearly reveals that alcohol abuse is by far the leading cause of liver-related mortality in the United States. Excessive alcohol consumption leads to three serious types of liver injuries: fatty liver (reversible), hepatic inflammation or alcoholic hepatitis (largely reversible with abstinence), and progressive liver scarring or cirrhosis (not reversible and ultimately may be fatal). Impaired liver functioning can cause primary hepatic encephalopathy, a brain disorder characterized by altered psychomotor, intellectual and behavioral functioning. Alcohol-related disease may take years to develop and the amount of drinking to cause damage varies. It is estimated that for men, it takes about ten drinks a day for 10 years but less than half that amount for women, before serious liver diseases are detected. The stages and progression of alcohol-related liver disease is shown in Table 10.4.

Withdrawal

Untreated alcohol withdrawal can range from flu-like symptoms to a life-threatening event. Early-stage withdrawal starts about 1–4 days after abstinence. In this phase, withdrawal symptoms and signs, include: transient visual or tactile hallucinations, irritability, tremor, insomnia, tachycardia, and convulsions. Late-stage withdrawal can occur quickly in 1–2 days in some people, but usually up to about 7 days after abstinence. During this phase,

Table 10.4 Stages of Alcoholic Liver Disease

State of disease	Cause or description	Consequences
Fatty liver (steatosis)	Alcohol metabolized over other energy sources leading to excess fat storage in liver. Extensive infiltration may alter liver function and extensive fatty liver may cause cell death.	Extensive infiltration may alter liver function and extensive fatty liver may cause cell death
Hepatitis (inflammation)	Prolific steatosis results in cell inflammation that can cause tissue damage	Significant recovery with abstinence
Cirrhosis (fibrosis)	Liver cells scarred and permanently damaged. Cell death follows.	Not reversible and a significant factor in alcohol-related death

withdrawal signs and symptoms include persistent hallucinations, cognitive impairment, agitation, delirium tremens, hypotension, diaphoresis (sweating) and fever. Tonic-clonic seizures may occur and may be minimized with prophylactic treatment with benzodiazepines.

Alcohol and the Fetus

In 1968, less than 10 years after the catastrophic birth effects of an anti-nausea drug thalidomide were recognized, scientists observed and documented a constellation of birth defects in the offspring of women who drank heavily during pregnancy. The broad constellation of signs and symptoms collectively define Fetal Alcohol Spectrum Disorder Children with FASD (see Figure 10.5) have distinct physical features, including craniofacial defects (e.g., small head circumference, epicanthal folds, small palpebral fissures, maxillary hypoplasia, thin upper lip) and overall are smaller in size and weight than non-alcohol exposed infants. Part of the difficulty in assessing this disorder is that the majority of children affected by alcohol do not show classic signs or symptoms and as a result, diagnosed with a less specific diagnosis of fetal alcohol effects (FAE), partial FAS (PFAS), or alcohol-related birth defects (ARBD). The term FASD reflects the continuum of effects on the alcohol exposed fetus. About half of all FASD children have some degree of developmental delay (IQs of less than 70) and other cognitive disorders including

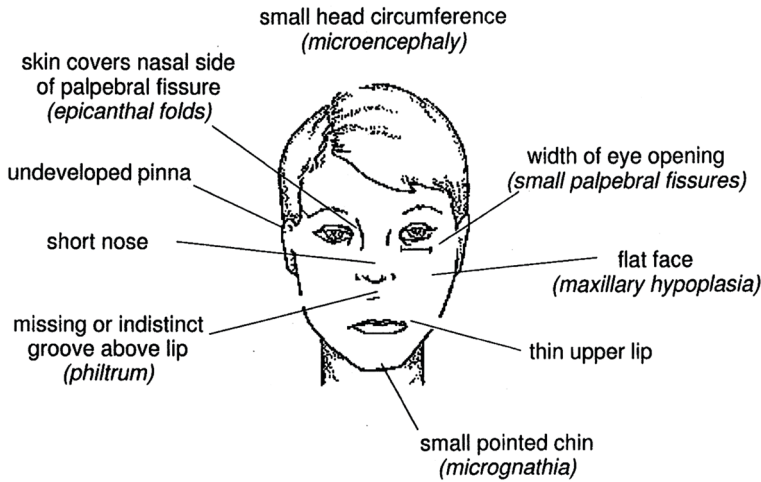


Figure 10.5 Craniofacial characteristics of FAS

hyperactive behavior, memory and attention difficulties, speech and language delays, poor reasoning and academic difficulties. Although physical features of the syndrome become less distinct with age, the psychological characteristics (e.g., poor interpersonal relationships, poor impulse control, intellectual developmental delay) do not diminish.

Estimates of the incidences of FASD in the United States vary based on where the information comes from. The Centers for Disease Control report FASD in 0.3 out of 1,000 children aged seven to nine based on medical and other records, whereas studies based on in-person assessment of school-age children place estimates at six to nine per 1,000 children. In some western European countries, estimates are much higher at one to five per 100 school children (or about 1 to 5 percent of the population). In experimental animals, large single doses of alcohol can produce many of the features of FAS, but no such cases of binge drinking-caused FAS have been documented in humans. Most medical authorities on the subject agree that there is no known safe dose of alcohol that can be consumed during pregnancy.

Forensic Considerations

The role of alcohol in crimes and accidents is greater than for any other psychoactive drug. Alcohol is legal, easily obtained and socially accepted by most people.

Driving while intoxicated is a serious medico-legal problem and accounts for nearly 14,000 motor vehicle fatalities per year of about 31 percent of all fatal crashes. The relative risk for a fatal motor vehicle crash due to alcohol intoxication is significantly greater than previously believed. Driving is impaired and risk increased at BACs well below the legal definition for intoxicated driving in the US (.08 percent).

Intoxication may also exacerbate death from certain head injuries in comparison to sober controls with similar head injuries. It is well known that alcohol is overly represented in domestic violence and other assaults, bicycling and water sports injuries and suicides. Alcohol (ethanol, methanol, isopropyl and other types of alcohol) is potentially fatal. Overdose deaths from alcohol poisoning occur about 2200 times a year in the United States. The greatest number of deaths occur among Hispanic whites but per population size, American Indians/Alaska Natives have the most poisoning deaths. No group or individual is immune from the toxic effects of alcohol if the dose is high enough. Pharmacokinetic and pharmacodynamic effects of alcohol as well as other drug effects should always be evaluated on a case-by-case basis.

Note

- 1 The term BAC refers to Blood Alcohol Concentration. BACs are expressed as grams% equivalent absolute ethanol in blood.

Selected Bibliography

- Abrahamo, K., Salinas, A. and Lovinger, D. (2017). Alcohol and the brain: Neuronal molecular targets, synapses and circuits. *Neuron*, 96(6): 1223–1238.
- Ahmed, N., Kuo, Y. H., Sharma, J. and Kaul, S. (2020). Elevated blood alcohol impacts hospital mortality following motorcycle injury. A National Trauma Data Bank analysis. *Injury*, 50(1): 91–96.
- Bagnardi, V., Rota, M., Botteri, E., Tramacere, I., Islami, F., Fedirko, V., Scotti, L., Jenab, M., Turati, F., Pasquali, E. and Pelucchi, C. (2015). Alcohol consumption and site-specific cancer risk: A comprehensive dose response meta-analysis. *British Journal of Cancer*, 112(3): 580–593.
- Banks, M. L. and Negus, S. S. (2017). Insights from preclinical choice models on treating drug addiction. *Trends in Pharmacological Sciences*, 2017 Feb;38(2): 181–194. doi: 10.1016/j.tips.2016.11.002. Epub 2016 Dec 2. PMID: 27916279; PMCID: PMC5258826.

- Bates, M., Brick, J. and White, H. (1993). The correspondence between saliva and breath estimates of blood alcohol concentration: Advantages and limitations of the saliva method. *Journal of Studies on Alcohol*, 54(1): 17–22.
- Brick, J. (1990). *Learning and motivational factors in alcohol consumption. Why people drink: Parameters of alcohol as a reinforcer*. Gardner Press, pp. 169–192.
- Brick, J. (1991, revised 1994). *Driving while intoxicated*. New Brunswick, NJ: Rutgers University Center of Alcohol Studies.
- Brick, J. (1995). *Fetal alcohol and drug effects*, New Brunswick, NJ: Rutgers University Center of Alcohol Studies.
- Brick, J. (2006). Interaction between toxicology and burn victim physiology. In A. Clark (Ed.), *Burns-The medical and forensic model*. Tucson, AZ: Lawyers and Judges Publishing Company, pp. 221–256.
- Brick, J. (2008). Medical consequences of alcohol abuse. In: J. Brick, *Handbook of the medical consequences of alcohol and drug abuse*. Haworth Press, Taylor & Francis Publishing, pp. 9–56.
- Brick, J. (2012). Alcohol: Use, tolerance and dependency. In *Wiley encyclopedia of forensic science*. Jamieson, A. and Moenssens, A. (Eds). 10.1002/9780470061589
- Brick, J. (2017). Alcohol use, tolerance and dependence. In: *Forensic alcohol test evidence*. C.C. Thomas, pp. 251–265.
- Brick, J. and Bennett, W. (2017). Alcohol calculations in emergency medicine. *Journal of Addiction Medicine and Therapeutic Science*, 3(3): 024–029. DOI:<http://doi.org/10.17352/2455-3484.000022>
- Brick, J., Adler, J., Cocco, K. and Westrick, E. (1992). Alcohol intoxication: Pharmacokinetic prediction and behavioral analysis. *Current Topics in Pharmacology*, 1: 57–67.
- Brick, J. and Erickson, C. (2009). Intoxication is not always visible: An unrecognized prevention challenge. *Alcoholism: Clinical and Experimental Research*, 33(9): 1489–1507.
- Brick, J., Wallen, M. and Lorman, W. (2012). Interaction of alcohol with medications and other drugs. Haworth Press/Taylor & Francis Group, pp. 527–564.
- Center of Alcohol Studies (1980). *Alco-calculator*, Alco-Research Documentation, Inc. New Brunswick, NJ: Rutgers University Center of Alcohol Studies.
- Chandler, C. M., Overton, J. S., Rüedi-Bettschen, D. and Platt, D. M. (2017). GABAA receptor subtype mechanisms and the abuse-related effects of ethanol: Genetic and pharmacological evidence. DOI:10.1007/164_2017_80
- Cocco, K., Adler, J. Westrick, E., Nathan, P. and Brick, J. (1986). Computerized program for the calculation of target blood alcohol levels in humans. *Proceedings and Abstracts of the Annual Meeting of the Eastern Psychological Association*, 57: 29.
- Davenport, H. (1971). *Physiology of the digestive tract*. Chicago: Yearbook Medical Publishers, pp. 163–173.
- Dawson, D. and Grant, B. (2011). The “gray area” of consumption between moderate and risk drinking. *Journal of Studies on Alcohol and Drugs*, 72: 453–458.

- Diagnostic and statistical manual of mental disorders, DSM-5-TR*, 5th Edition. (2022). Washington, DC: American Psychiatric Association.
- Dubowski, K. M. (1985). Absorption, distribution and elimination of alcohol: Highway safety aspects. *Journal on Studies of Alcohol Supplement*, 10: 98–108.
- Fox, D., Pettygrove, S., Cunniff, C., O’Leary, L., Gilboa, S., Bertrand, J., Druschel, C., Breen, A., Robinson, L. Ortiz, L. and Frias, J. (2015). Fetal alcohol syndrome among children aged 7–9 years – Arizona, Colorado and New York. 2010. *MMWR Morbidity and Mortality Weekly Report*, 64(3): 54–57.
- Frezza, M., DiPadova, C., Pozzato, G., Terpin, M., Baraona, E. and Lieber, C. S. (1990). High blood alcohol levels in women: The role of decreased gastric alcohol dehydrogenase activity and first-pass metabolism. *New England Journal of Medicine*, 322(2): 95–99.
- Gillman, M., Cook, N., Evans, D., Rosner, B. and Hennekens, C. (1995). Relationship of alcohol intake with blood pressure in young adults. *Hypertension*, 25(5): 1106–1110.
- Haggard, H. W., Greenberg, L. A. and Cohen, L. H. (1938). Quantitative differences in the effects of alcoholic beverages. *New England Journal of Medicine*, 219: 446–470.
- Harger, R. N. and Forney, R. B. (1963). Aliphatic alcohols. In: A. Stolman (Ed.), *Progress in chemical toxicology*. New York: Academic Press, p. 79.
- Hendrix, T. (1974). The motility of the alimentary canal. In: V. B. Mountcastle (Ed.), *Medical physiology*, Vol. 2, St. Louis, MO: C. V. Mosby, pp. 1208–1236.
- IARC Working Group on the Evaluation of Carcinogenic Risks to Humans (2010). Alcohol consumption in and ethyl carbamate. IARC Monographs on the Evaluation of Carcinogenic Risks in Humans 2010, 96: 3–1383.
- Johnson, L., O’Malley, P. and Bachman, J. (1996). *Monitoring the future study 1975–1996*. Rockville, MD: USDHHS, National Institute on Drug Abuse.
- Johnston, L. D., O’Malley, P. M., Bachman, J. G. and Schulenberg, J. E. (2011). *Monitoring the future national survey results on drug use, 1975–2010: Volume II, College students and adults ages 19–50*. Ann Arbor: Institute for Social Research, The University of Michigan.
- Kalant, H. (1971). Absorption, diffusion, distribution an elimination of ethanol: Effects on biological membranes. In: B. Kissin and H. Begleiter (Eds), *The biology of alcoholism*, Vol. 1, *Biochemistry*, New York: Plenum Press, pp. 1–46.
- Lamb, R. J. and Ginsburg, B. C. (2018). Addiction as a BAD, a Behavioral Allocation Disorder. *Pharmacology Biochemistry and Behavior, Decision Making in Addiction*, 164: 62–70. <https://doi.org/10.1016/j.pbb.2017.05.002>DBB 3 Alcohol.doc
- Lamb, R. J., Stark, H. G., Ginsburg, B. C. (2021). Implications of there being many paths to addiction and recovery. *Pharmacology Biochemistry and Behavior*, 2021 Dec; 211: 173299. doi: 10.1016/j.pbb.2021.173299. Epub 2021 Nov 12. PMID: 34780878.
- Langenbucher, J., McCrady, B., Brick, J. and Esterly, R. (1993). *Socioeconomic evaluations of addictions treatment*. Washington, DC: The White House, President’s Commission on Model State Drug Laws.

- Litovitz, T. L., Klein-Schwartz, W., Caravatai, E., et al. (1998). 1997 Annual Report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. *American Journal of Emergency Medicine*, 16(5): 443–497.
- Luna, G., Maier, R., Sowder, L., Copass, M. and Oreskovich, M. (1984). The influence of ethanol intoxication on outcome of injured motorcyclists. *The Journal of Trauma*, 24(8): 695–700.
- Martin, C. and Moskowitz, H. (1993). Measurement of acute tolerance to alcohol in human subjects. *Alcoholism: Clinical and Experimental Research*, 17(2): 211–216.
- Martin, T., Solbeck, P., Mayers, D., Langille, R., Buczek, Y. and Pelletier, M. (2013). A review of alcohol-impaired driving: The role of blood alcohol concentration and complexity of the driving task. *Journal of Forensic Sciences*, 2013 Sep; 58(5): 1238–1250. doi: 10.1111/1556-4029.12227. Epub 2013 Jul 23. PMID: 23879433.
- Mattson, S., Roesch, S., Fagerlund, A., Autti-Ramo, I., Jones, K., May, P., Adnams, C., Konovalova, V., Riley, E. P. and the CIFASD (2010). Toward a neurobehavioral profile of fetal alcohol spectrum disorders. *Alcoholism: Clinical and Experimental Research*, 34(9): 1640–1650.
- May, P., Chambers, C., Kalberg, W., Zellner, J., Feldman, H., Buckley, D., Kopald, D., Hasken, J.M., Xu, R., Honerkamp-Smith, G. and Taras, H. (2018). Prevalence of fetal alcohol spectrum disorders in 4 US communities. *JAMA*, 319(5): 474–482.
- May, P., Gossage, J., Kalberg, W., Robinson, L., Buckley, D., Manning, M. and Hoyme, H. (2009) Prevalence and epidemiologic characteristics of FASD from various research methods with an emphasis of recent in-school studies. *Developmental Disabilities Research Reviews*, 15: 176–192.
- Moskowitz, H. and Robinson, C. D. (1988). Effects of Low Doses of Alcohol on Driving-Related Skills: A Review of the Evidence. <https://doi.org/10.21949/1525245>
- National Institute on Alcohol Abuse and Alcoholism (NIAAA). (2000). *Tenth Special Report to the U.S. Congress on Alcohol and Health from the Secretary of Health and Human Services*. Rockville, MD: US Department of Health and Human Services Public Health Service, National Institute of Health, National Institute on Alcohol Abuse and Alcoholism.
- Niaura, R. S., Nathan, P. E., Frankenstein, W., Shapiro, A. P. and Brick, J. (1987). Gender differences in acute psychomotor, cognitive, and pharmacokinetic response to alcohol. *Addictive Behaviors*, 12: 345–356.
- Nimitvilai, S., Arora, D. S., McElvain, M. A., Brodie, M. S. (2012). Ethanol blocks the reversal of prolonged dopamine inhibition of dopaminergic neurons of the ventral tegmental area. *Alcoholism: Clinical and Experimental Research*. DOI: 10.1111/j.1530-0277.2012.01814.x
- Palmer, R. (1994). Cimetidine and alcohol. *Drug Investigation*, 8(1), 63–65.
- Palmer, A., Fletcher, A., Bulpitt, C., Beevers, D., Coles, E., Ledingham, J., Petrie, J. C., Webster, J. and Dollery, C. T. (1995). Alcohol intake and cardiovascular mortality in hypertensive patients: Report from the Department of Health Hypertension

- Care Computing Project. *Journal of Hypertension*, 1995 Sep; 13(9): 957–964. DOI: 10.1097/00004872-199509000-00004. PMID: 8586830.
- Pohorecky, L. and Brick, J. (1990). The pharmacology of ethanol. In: D. Balfour (Ed.), *International encyclopedia of pharmacological therapeutics: Psychotropic drugs of abuse*. Elmsford, NY: Pergamon Press, pp. 189–281.
- Pompili, M., Serafini, G., Innamorati, M., Dominici, G., Ferracuti, S., Kotzalidis, G. D., Serra, G., Girardi, P., Janiri, L., Tatarelli, R., Sher, L. and Lester, D. (2010). Suicidal behavior and alcohol abuse. *International Journal of Environmental Research and Public Health*, 2010 Apr; 7(4): 1392–1431. DOI: 10.3390/ijerph7041392. Epub 2010 Mar 29. PMID: 20617037; PMCID: PMC2872355.
- Smith, G., Keyl, P., Hadley, J., Bartley, C., Foss, R., Tolbert, W. and McKnight, J. (2001). Drinking and recreational boating fatalities. *JAMA*, 286(23): 2974–2980.
- Smyth, A., O'Donnell, M., Rangarajan, S., Hankey, G., Oveisgharan, S., Canavan, M., McDermott, C., Xavier, D., Zhang, H., Damasceno, A. and Avezum, A. (2022). Alcohol intake as a risk factor for acute stroke. *Neurology*, 100(2): e142–e152; DOI: 10.1212/WNL.0000000000201388
- Surgeon General's Workshop on Drunk Driving (1988). US Department of Health and Human Services, Office of the Surgeon General, p. 139, Washington, DC.
- Taylor, B. and Rehm, J. (2012). The relationship between alcohol consumption and fatal motor vehicle injury: High risk at low alcohol levels. *Alcoholism: Clinical and Experimental Research*. DOI: 10.1111/j.1530-0277.2012.01785.x
- US Department of Health and Human Services and US Department of Agriculture (2010). *Dietary Guidelines for Americans, 2010*. 7th Edition, Washington, DC: US Government Printing Office. Available at <http://www.cnpp.usda.gov/Publications/DietaryGuidelines/2010/PolicyDoc/PolicyDoc.pdf>. Last accessed May 6, 2012.
- US Department of Transportation, National Highway Traffic Safety Administration (1988). *Effects of low doses of alcohol on driving-related skills: A review of the evidence*, DOT HS 807 280 (1988), pg. 67
- Vandaele, Y. and Ahmed, S. H. (2021). Habit, choice, and addiction. *Neuropsychopharmacology*, 46: 689–698. <https://doi.org/10.1038/s41386-020-00899-y>
- Vogel-Sprott, M. (1979). Acute recovery and tolerance to alcohol: Differences in cognitive and motor skill performance. *Psychopharmacology*, 61: 287–291.
- Von Wartburg, J. (1989). Pharmacokinetics of alcohol. In: K. P. Crow and R. P. Batt (Eds), *Human metabolism of alcohol*. Boca Raton, FL: CRC Press, pp. 9–22.
- Waller, P., Steward, J., Hansen, A., Stutts, J., Popkin, C. and Rodgman, E. (1986). The potentiating effects of alcohol on driver injury. *JAMA*, 256(11): 1461–1466.
- Watson, P. E. (1989). Total body water and blood alcohol levels: Updating the fundamentals. In: K. Crow and R. Batt (Eds), *Human metabolism of alcohol*. Boca Raton, FL: CRC Press, pp. 41–58.
- Widmark, E. (1981). *Principles and application of medicolegal alcohol determination*. CA: Biomedical Publications, pp. 47–82.

- Wilkinson, P. K. (1980). Pharmacokinetics of ethanol: A review, *Alcoholism: Clinical and Experimental Research*, 4: 6–21.
- Wilson, G. T., Brick, J., Adler, J., Cocco, K. and Breslin, C. (1989). Alcohol and anxiety reduction in female social drinkers. *Journal of Studies on Alcohol*, 50(3): 226–335.
- Yoon, Y-H., Stinson, F., Yi, H-Y. and Dufour, M. (2004). Accidental Alcohol Poisoning Mortality in the United States NIAAA. Available at <http://pubs.niaaa.nih.gov/publications/arh27-1/110-120.htm>. Last accessed December 2010.
- Zhao, H., Mayhan, W., Arrick, D., Xiong, W and Sun, H. (2010). Alcohol-induced exacerbation of ischemic brain injury: Role of NAD(P)H oxidase. *Alcoholism: Clinical and Experimental Research*, 34(11): 1948–1955.
- Zhu, W., Volkow, N., Ma, Y., Fowler, J. and Wang, G-J. (2004). Relationship between induced changes in brain regional metabolism and its motor, behavioral and cognitive effects. *Alcohol & Alcoholism*, 39(1): 53–58.
- Zink, B., Maoi, R. and Chen, B. (1996). Alcohol, central nervous system injury, and time to death in fatal motor vehicle crashes. *Alcoholism: Clinical and Experimental Research*, 20(9): 1518–1522.
- Zink, B. J., Schultz, C. H., Stern, S. A., Mertz, M., Wang, X., Johnston, P. and Keep, R. F. (2001). Effects of ethanol and naltrexone in a model of traumatic brain injury with hemorrhagic shock. *Journal of Clinical & Experimental Research*, 25(6): 916–923.

Opioids: Drugs That Calm Our Pain

11

Opioids are natural and synthetic derivatives of morphine and include commonly used and overused drugs such as fentanyl, heroin, oxycodone, codeine, etc. The prototype of these drugs is morphine, which has historically been used as a cure-all. Morphine, codeine, fentanyl and oxycodone are powerful narcotic analgesics with medical uses ranging from pain relief to cough and diarrhea remedies and in surgery. The illicit use of fentanyl and related synthetic opioids have eclipsed all others and is particularly dangerous. The study of opioids has provided more pieces of the “puzzle” than any other area of psychopharmacology research. The most exciting fact about this class of drugs is that they work through the excitation of brain receptors that are also affected by naturally occurring opioids called endorphins. These brain chemicals are probably involved in determining our natural pain threshold, our exercised-induced “high”, and our response to addicting drugs. In this chapter, we will explore the characteristics of different types of opioids, including their medical therapeutic use, illegal use, misuse and dependence potential in illegal situations, with heroin as the prototype opioid used “on the street”. We will also study how receptor agonists and antagonists are used as antidotes to opioid overdose, for the treatment of opiate addicts, and for the treatment of alcohol-dependent patients.

History of Opiate Use

Evidence of opiate use in what is now part of Europe and the Middle East goes back approximately 6,000 years. Opiates have been used as a cure-all for various

diseases ranging from organic medical disorders to depression. Opiate use was widespread and opium was readily available for self-medication during the time of Hippocrates, the father of medicine (circa 470–370 BC). Opiates were a valuable commodity and as the opium trade grew, their use spread throughout Europe. Opium was generally considered a panacea for all human problems. People from various walks of life patronized “opium dens” where they could enter the dreamworld produced by this drug. As a narcotic analgesic, opium was unsurpassed in its ability to decrease the response to pain, to suppress coughing and to treat dysentery. Until the mid-1800s, opiates were the most effective surgical anesthetics available and of such value that, in 1839, the First Opium War broke out over trading rights between China and Great Britain.

It was not until about 1806 that Frederich Sertürner, a German pharmacist, isolated the primary active ingredient in opium and named it morphium after the Greek god of dreams, Morpheus. In 1832 codeine was similarly identified as the other psychoactive compound in opium. The identification of these compounds, coupled with the invention of the hypodermic syringe in the early 1850s, was enormously helpful in treating severe pain but increased the incidence of addiction. Intravenous morphine was used regularly throughout the various wars of the 19th century including the American Civil War (1861–1865), the Prussian-Austrian War (1866) and the Franco-Prussian War (1870). Because the use of opiates was not regulated and they were available without prescription, returning veterans who had become addicted were able to maintain their addiction. Opiate addiction thus became known at the time as “soldier’s disease”.

During the 19th century, physicians were few and medical treatments were rather limited (as was medical knowledge in general). To meet this need, a new industry emerged that promoted the use of various opiate-based tonics and elixirs, such as laudanum, a popular concoction of opium, wine, and various spices. These were inexpensive, socially acceptable, and effective in relieving aches, pains, nervousness, diarrhea, and coughing, but they were nonetheless addictive because their primary active ingredients were opiates. Concern over the growing number of opiate addicts in the United States led to the development of the 1906 Food and Drugs Act and eventually the Harrison Narcotic Act, which mandated, among other things, a physician’s prescription in order to obtain the drug. Deaths from opioid overdoses have tripled in the United States between 1999 and 2006 – from about 4,000 to nearly 15,000 deaths per year and in 2020, opioid overdoses reached 69,000 (more than 82 percent of which involved synthetic opioids). In 2022, the number of opioid fatalities exceeded 100,000. There exists a crisis of epidemic proportion.

What Are Opioids?

An “opiate” is now considered an older term used to describe drugs derived from opium and include morphine, codeine, and semi-synthetic compounds derived from them, such as heroin, oxycodone, and hydrocodone. Although the term opiates is still in use, more recently, it has been replaced with the broader term opioids, which includes all agonists and antagonists with morphine-like activity, and including chemicals ranging from naturally occurring opioid peptides such as endorphins to completely synthetic opioids such as methadone, tramadol and fentanyl to be discussed later.

Sometimes opioids (and opiates) are referred to as narcotics, from the Greek word *narko* (meaning to make numb) because they produce sleepiness or a dreamlike state also called a “nod” or stupor. Because of the Harrison Narcotic Act of 1914, which included marijuana and cocaine as narcotics, many legal statutes still use the term narcotic to include drugs that are not opioids. This is incorrect. For example, describing cannabinoids as narcotics creates an inference that cannabis is related to more highly addictive and dangerous drugs such as fentanyl or heroin. This problem frequently occurs when people with legislative influence make decisions without consulting scientific experts. The four families of opioids (natural, semi-synthetic, synthetic and endogenous opioid peptides) are discussed below.

Natural Opiates

Opium and codeine are natural opiates derived from *Papaver somniferum*, a vibrantly beautiful flowering plant that blooms annually. The plants grow to a height of three or four feet and have large flowers (4" to 5" in diameter) of various colors, including white, pink, red, purple, or violet. The harvesting of raw opium (see Figure 11.1) is an ancient but interesting process somewhat similar to the traditional collection of maple sap. After the petals of the flower drop off, but before the large seedpod matures, the seedpod is scored (lightly cut). Overnight, a white substance appears, which, when it makes contact with the air, oxidizes to a gummy reddish-brown resin. The resin is raw opium, which is scraped from the outside of the pod and can be smoked, eaten, or refined as desired. Industrial harvesting of morphine is the poppy straw process in which morphine is extracted from the mature dried plant (the straw).



Figure 11.1 Harvesting of raw opium from the poppy plant (*Papaver somniferum*)

Opium – The Natural Opioid

Raw opium found in the exudate from the poppy plant contains morphine, codeine and other alkaloids including papaverine and thebaine. Opium in this form has been eaten or smoked for thousands of years. By the 19th century chemists identified a specific component of opium, identified as morphine, named after Morpheus the Greek god of sleep. Scientists began experimenting with synthetic and semi-synthetic forms of morphine that were more potent analgesics. Morphine is still the prototypical narcotic analgesic and the standard against which the potency of other opioids is judged.

Semi-Synthetic Opioids

The widespread use, analgesic effectiveness, and potential for an ever-growing market led to additional research on the chemistry of opiates. In

the late 1800s, it was found that adding two acetyl groups to the morphine molecule changed it to another compound, heroin. This new drug, diacetylmorphine, was introduced by Bayer Laboratories in 1898 and marketed as a nonaddicting pain reliever called heroin (see Figure 11.2). The addition of the two acetyl groups (COCH_3) to the morphine molecule significantly

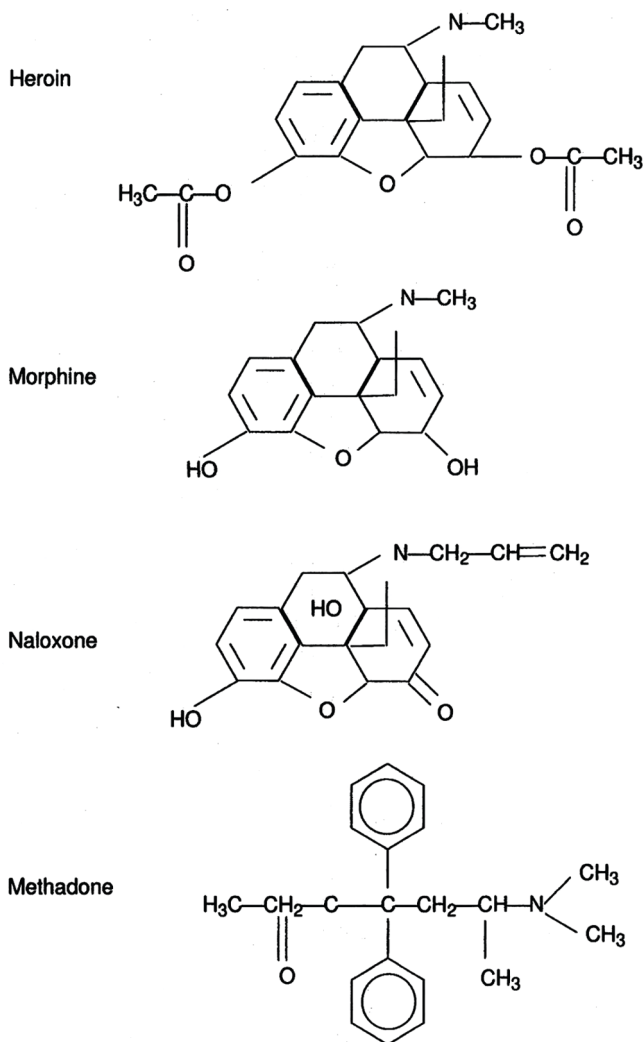


Figure 11.2 Chemical structures of various opioids and the opioid antagonist naloxone

increased the drug's lipid solubility, enabling it to pass through the blood-brain barrier more rapidly. Once in the brain, heroin goes through a biotransformation and is converted to morphine. The biobehavioral effects of heroin and morphine are identical, but heroin is about two to three times more potent and has a more rapid onset. Both heroin and morphine are highly addicting drugs.

Other semi-synthetic opioids such as oxycodone have gained widespread popularity in the medical management of pain. These drugs (Trade names for oxycodone: Oxycontin, Roxicodone) are often formulated with acetaminophen and marketed as Percocet or with aspirin and marketed as Percodan. Vicodin is a popular combination of hydrocodone, another semi-synthetic opioid, and acetaminophen. Oxycodone, hydrocodone, and other semi-synthetic opioids (of which there are many) are widely overused and are highly addictive. Oxycodone and hydrocodone misuse have increased dramatically in recent years and have been implicated in a number of high-profile drug overdose cases.

Synthetic Opioids

Methadone was developed during the Second World War by the Germans in response to decreased supplies of morphine and other anesthetics needed during wartime. Named Dolophine, after Adolf Hitler, methadone is frequently administered orally to treat acute and chronic pain, and heroin addicts. Methadone itself is addicting and psychoactive. However, when administered in a controlled clinical setting for treating heroin addicts, it a) reduces the need to procure the drug on the street, b) in high doses will block the euphoria normally produced by heroin, c) eliminates risks associated with needle sharing (e.g., HIV, hepatitis) and d) allows the addicted person to engage in meaningful employment. While it is a powerful pain reliever, the recreational use of methadone has led to a large number of overdose deaths. Methadone (Figure 11.2) has a particularly long half-life (15–55 hours), which may contribute to overdose when multiple doses are administered.

Tramadol (with acetaminophen, called Ultracet) and meperidine (Demerol) are other commonly used synthetic opioids but with much shorter half-lives than methadone (see Table 11.1). Tramadol is equipotent with codeine whereas meperidine is about one tenth the potency of morphine. Relative potencies vary based on many factors.

Table 11.1 Pharmacological Characteristics of Common Opioids

Drug (brand name)	Approx onset* (min)*	Approx. duration (hrs)	Half-life (hrs)	Potency relative to morphine	Speed of action
Codeine	25*	5	2–4	0.1×	Onset of effect or peak effect significantly varies with administration route and formulation
Heroin***	15	4–5	0.03–0.1	up to 5×	
Meperidine (Demerol)	15*	3	2–5	0.1×	
Morphine (MS Contin)	20*	7	1–7**	1	
Hydromorphone (Dilaudid)	25*	4–5	2–4	5–10×	Intravenous injection is fastest, followed by transmucosal, transdermal, and intra muscular. Oral (gastro-intestinal) is the slowest
Methadone (Dolophine)	10–15*	4–6	15–55 (variable)	1×	
Fentanyl (Duragesic, Abstral, Antiq)	5–10	0.3–0.5	3–12	100×	
Carfentanil (Wildnil)			0.75–6	10,000×	
Oxycodone (Oxycontin)	10–30*	3–6	4–6	1–2×	

* Oral administration.

Transdermal, sublingual or intranasal less than ten minutes. By injection, less than two minutes.

** 15–16 hours for modified release preparations.

*** Heroin is very rapidly metabolized (within 2–3 minutes). Most of its effects are due to its metabolite, morphine.

Up until about 20 years ago opioid use was a fraction of that of other psychoactive drugs but in the last 10 years, use of opioids has increased significantly, particularly during the COVID 19 pandemic. Fentanyl use has increased dramatically and in the United States has reached epidemic proportions.

Fentanyl, and fentanyl analogs (e.g., acetyl fentanyl, 3-methylfentanyl, alphamethylfentanyl, furanyl fentanyl) are structurally different from morphine but still act on the opioid *mu*-receptor and like other opioids, have analgesic effects. Fentanyl is widely used in medicine for pain management and surgery. Fentanyl has significant respiratory depressant effects which likely explains, in part, how their use is life-threatening, particularly when used recreationally and not under medical supervision. Fentanyl is about 200 times more potent than morphine or heroin or any other opioids and fentanyl analogs such as sufentanil is estimated to be 4,000 times more potent than morphine and carfentanil is about 10,000 times more potent. When taken in combination with other drugs (e.g., mixed with heroin) fentanyl and fentanyl analogues are extremely dangerous and when taken alone too often results in a fatal overdose. About 80 percent of more than 75,000 opioid deaths in the United States are due to fentanyl overdose and is considered to constitute an opioid epidemic.

Where Does Fentanyl Come From?

Fentanyl is used under medical supervision for severe pain management (pharmaceutical fentanyl) or manufactured illegally. Sources for the illegal manufacture of fentanyl change in response to ongoing law enforcement efforts that force manufacturers to move to different countries. Regardless of the source, large amounts of fentanyl (11,000 pounds in 2022 alone) are smuggled into the United States through the southern border. Drug cartels readily distribute this drug online, through social media and via direct sales. The United States has been struggling with this crisis for a decade and accounts for about 20 percent of world distribution of fentanyl, followed by Germany and the United Kingdom. Recent data from the U.S. Center for Disease Control indicates synthetic opioids like fentanyl are responsible for about 150 overdose deaths per day.

Endogenous Opioid Peptides

In what might be considered the Rosetta stone of modern neuropharmacology, an amazing discovery was made in the early 1970s that answered the question, “why would the body respond to opioids at all?”. After all, these compounds are psychoactive, addictive, do not promote health and can be toxic. Although scientists knew that drugs produced their effects by affecting neurons in the brain, it was in 1973 that the discovery of endogenous (“from within”, naturally-occurring) opiate receptors in the central nervous system changed everything. Subsequent studies have found opioid receptors in the gastrointestinal and other systems. Why would the body have such highly specific receptors?

The answer to this question is now obvious. If specific opiate receptors exist endogenously (in the organism), then the body itself must produce compounds that are very similar to exogenous (outside the organism) opioids. The first two endogenous opioid peptides to be discovered were short-chained amino acid sequences named leucine-enkephalin and methionine-enkephalin. This discovery was soon followed by the discovery of a beta-endorphin, a long thirty-one-amino-acid peptide whose first five amino acids were identical to methionine-enkephalin. Other brain peptides involved in modulation of pain responses are known as dynorphins. Collectively, enkephalins, beta-endorphins, and dynorphins are part of a family of endogenous opioid-like peptides known as “endorphins”, or “naturally” occurring morphine-like substances. It is now clear that various endorphins are manufactured within the limbic system, brain stem, pituitary gland and can be found in many other organ tissues including the adrenal gland, gastrointestinal tract, the heart and pancreas. These endogenous opioid peptides act as part of the body’s natural response to pain. For example, plasma endorphin levels increase during childbirth, traumatic accidents and running. The latter may explain, in part, the “runner’s high” frequently reported by athletes. The discovery of endogenous receptors for drugs that make people high has provided a roadmap for research on endogenous receptors for other drugs.

Administration, Absorption, Distribution, Metabolism/Elimination

Administration and Absorption

Just as with other drugs, opioids can be administered via the four most common routes. Each has advantages and disadvantages.

1. *Oral*: The oldest route of opiate administration is oral. Opium cakes, candies, and various tonics containing the drug are traditional routes of administration. Because of the relatively low lipid solubility of naturally occurring opiates, oral administration is, although effective, not efficient in terms of maximum bioavailability. Methadone, a synthetic narcotic analgesic, is also administered orally in liquid form
2. *Pulmonary*: Interestingly, the widespread use of opium in China was tolerated well before the first millennium, but tobacco smoking was considered to be foul and offensive. By 1644 the Chinese emperor banned tobacco but not opium smoking in China. Because of the tobacco ban (which incidentally was very short-lived) opium smoking rapidly became a very popular and rapid method of administration
3. *Insufflation*: Powdered opium and heroin can be insufflated (“snorted”) and absorbed through the nasal membranes. Although opium is not well absorbed by this route, it is a frequently used method for first-time users. However, heroin and fentanyl have high lipid solubility allowing these opioids to enter the circulation rapidly through transmucosal insufflation. Various opioids are available as a liquid, or other water-soluble narcotics can be injected using all three injection sites: intravenous, intramuscular, and subcutaneous

Distribution

All opioids are distributed throughout the body, including the central nervous system where they exert their psychoactive effects. Natural opiates, because of their relatively low lipid solubility, generally do not enter the brain as quickly as semi-synthetic opioids such as heroin. As with other drugs, if the opioid is smoked or injected IV, it enters the circulation almost immediately, with high blood concentrations occurring within minutes.

Metabolism and Elimination

Opioids are metabolized primarily by CYP enzymes the liver. Most opioids have a duration of action of about four to six hours since the half-life of most is relatively short, approximately three to four hours but there are some rather dramatic exceptions. For example, the half-life of methadone is quite long, at about 15 to up to 55 hours and fentanyl has a half-life of

3 to 12 hours. In comparison, the half-life of heroin is only a few minutes (and is rapidly metabolized to morphine). Reported pharmacokinetics of opioids vary based on many factors including route of administration, formulation (e.g., immediate vs extended-release tablets) and duration of use (repeated dosing is sometimes required to obtain a steady state concentration) and individual pharmacokinetics (some opioids have one or two elimination phases). Table 11.1 lists the most common opioids and their known characteristics.

Pharmacology of Opioids

Opioids exert their effects through specific receptors in the brain, spinal cord, and elsewhere. The four primary groups of opioid receptors are designated by the Greek letters, *mu* (μ) kappa (κ) and delta (δ), and FQ nociceptin. Each receptor is specific to endogenous peptides (enkephalins and endorphins) but it is the *mu* receptor that is activated by most exogenous opioids. Codeine, heroin, hydrocodone, morphine, oxycodone and other opioids are *mu* agonists, and all exert their analgesic and intoxicating effects only through the *mu* receptor. Kappa receptor agonists also produce analgesia, sedation, and dysphoria but without the potentially dangerous respiratory depression that *mu* agonists produce. Pentazocine (Talwin), for example, is an opioid with mixed kappa, *mu*, and delta receptor agonist properties. Most opioids are *mu* receptor agonists or partial agonist-antagonists at *mu* and kappa receptors.

Opioid Antagonists

Opioid antagonists are drugs that displace opiates and related compounds from their receptor sites, and occupy receptors without producing an action on the receptor. When these drugs are administered prophylactically, opiates are not able to produce intoxication. These antagonists are so effective in displacing opiates that they are effective in treating toxic overdoses. Naloxone (Narcan) is used for this purpose. Within seconds of intravenous administration, comatose patients with opioid overdoses rapidly regain consciousness. Naltrexone (ReVia, formerly Trexan) is a longer-acting antagonist used in the treatment of heroin and alcohol dependence.

Biobehavioral Effect of Opioids

The euphoric effects of opioids begin shortly after the drug enters the circulation. If the drug is injected intravenously, the subjective rush is followed by a warming sensation, dry mouth, and heavy peripherals (limbs) and an alternating mental state; the user becomes drowsy and moves in and out of consciousness. It is common for the eyes to close and the head to slowly nod forward as the user drifts in and out of their opioid stupor. This drowsy condition is referred to as being “on the nod”. Speech becomes slurred and raspy, eyelids become heavy. Table 11.2 lists the common effects seen when opioids are administered.

In addition to the common signs of intoxication listed in Table 11.2, cyanosis (bluish discoloration of skin due to lack of oxygen), edema (swelling of feet, ankles, legs due to fluid accumulation), seizures and coma should be considered signs of a potentially fatal overdose. These signs require immediate intervention. Naloxone is the standard treatment for opioid overdose and should be administered as quickly as possible. First Responders will have, and family members of at-risk persons may obtain, naloxone from their physician or pharmacist. Intranasal (transmucosal) or intramuscular naloxone has a rapid onset and should be administered prior to arrival at a hospital.

Table 11.2 Signs and Symptoms of Opioid Intoxication

-
- Constricted pupils (miosis)
 - Decreased pulse (bradycardia)
 - Decreased temperature
 - Decreased respiration
 - Slowed reflexes
 - Muscular rigidity
 - Slow, low, raspy, slurred speech
 - Vertigo, dizziness
 - Skin cool to the touch
 - Nausea (new users)
 - Impaired memory and attention
 - Decreased response to pain
 - Sedation
 - Stupor or coma (overdose)
-

Medical Uses

The primary medical use of opioid analgesics such as morphine is in the treatment of moderate to severe pain. Opioids are extremely effective in reducing the affective (“suffering”) component of pain. When under the influence of these drugs, people know the pain is there but do not respond to it. Morphine, oxycodone, tramadol, and related opioids are frequently prescribed for this purpose. Opioids, usually in the form of codeine, are very effective in treating coughs, although synthetic derivatives such as dextromethorphan (a synthetic analogue of codeine) are also effective without the sedating and addicting properties.

Medical Consequences

Overall, opioids have far fewer direct medical consequences than other drugs of abuse. In comparison to many other psychoactive drugs (e.g., alcohol, stimulants, steroids, nicotine), opioids have relatively few medical consequences or direct toxic effects on tissues or organs. That does not mean that opioid analgesics are safe! They have a high potential for addiction and overdose, and adulterants used to cut drugs are the primary causes of necrosis (cell death). Opioids decrease the activity of those brainstem regions that monitor blood CO₂ but also stimulate those neurons in the medulla that are part of the vomit reflex. As a result, users experience nausea from drugs such as heroin until they develop tolerance.

Opioid use can also cause immediate death due to acute hypersensitivity, sometimes described as an anaphylactoid reaction. This reaction is caused by the well-known effect of opioids on mast-cell degranulation and subsequent histamine release in the lungs. Histamines trigger an allergic-like reaction leading to pulmonary edema (buildup of fluid in the lungs), decreased blood pressure, and respiratory depression. Although true allergic-like reactions to heroin or morphine are probably rare, pulmonary edema from opioid overdose is probably the most common cause of overdose deaths. Infections, including the transmission of the HIV virus from shared needles, also contribute to illness and death in this population. Less common lethal effects are positional asphyxia that occurs when the rapid onset of sedation places the acutely intoxicated person at risk for slumbering into a position in which breathing is restricted.

The toxic effects of problem opioid use and addiction include direct and indirect medical consequences. Indirect effects are primarily with regard to viral (e.g., HIV, Hepatitis B or C), bacterial, and fungal infections related to

intravenous drug use (shared needles, nonsterile conditions, etc.) The more serious problem is the epidemic of opioid overdose fatalities in recent years. In the United States alone, annual opioid deaths far exceeded the number of deaths from drunk driving accidents and gun-related violence combined! It is estimated that 70–80 percent of opioid overdose cases involve fentanyl. Other indirect toxic consequences include the inadvertent use of cutting agents. For example, talcosis is a syndrome that occurs when talc, or similar powdery material, is used to adulterate heroin. Talc or other insoluble substances lodge in capillary beds in the lungs, kidneys, or other organs, resulting in various pathologies. Death from opioid overdose is a serious medical consequence.

Opioids and the Fetus

Pregnant women who are addicted to heroin place their fetuses at risk should they go through withdrawal or when they give birth, because the abrupt termination of the drug to the child may be very stressful. Children born to heroin-addicted mothers are restless, irritable, and tremulous, and have a high-pitched cry, gooseflesh, runny nose and other adult-like withdrawal symptoms. In addition, such infants are smaller in overall size and head circumference than control subjects of mothers not using heroin. Newborns undergoing withdrawal from opiates and methadone are classified as having Neonatal Abstinence Syndrome (NAS).

Methadone, when used to treat heroin dependent patients, is a relatively safe alternative to heroin, but it is still an addictive drug. Compared to control subjects (children whose mothers did not take methadone), methadone-exposed infants have poorer fine and gross motor coordination at birth. By age five, these children are more active, engage in task-irrelevant activity, and have poorer fine-motor coordination than controls. There are conflicting reports regarding the effects of prenatal opioid exposure on cognitive development in toddlers and preschoolers. Observations of delayed mental and motor development may be due to poor environmental conditions, or methadone may produce subtle neurological changes, making children more susceptible to the developmental delays associated with impoverished environments. Finally, mothers who use heroin or methadone often use other drugs (nicotine, etc.), which have well known effects on fetal development particularly low birth weight. Such fetuses are often poorly nourished and receive poor prenatal care. Thus, many factors may contribute to fetal distress before and after birth.

Tolerance and Dependence on Opioids

Tolerance to some of the effects of opiates develops within only a few days of use and increases throughout the addiction process. Opioid tolerance is often quite remarkable. Whereas a usual low dose (milligrams) is sufficient to produce euphoria in most people, some chronic opioid users will require very high doses (grams) to produce an effect. This is also illustrated in clinical cases where, there may be little or no observed impairment when intoxicated or after a patient is treated with chronic opioids for pain management. Tolerance develops to the euphoric and analgesic effects of analgesics as well as to some of the side effects (nausea). Tolerance does not develop to pupil constriction and only slight tolerance develops to the constipating effects of these drugs. Among chronic addicts, even high doses of the drug will produce little pleasurable effect because of tolerance. In those instances, the drug is taken primarily to avoid the consequences of withdrawal. It is a vicious cycle.

Opioids, regardless of their origin (natural, semi-synthetic, synthetic), produce physical dependence. The regular use of these drugs produces withdrawal symptoms upon cessation of use. Withdrawal from narcotic analgesics is very rarely life threatening but it is very unpleasant. The multiple symptoms of withdrawal are similar to a very severe bout of influenza and occur about 6 to 12 hours after the last dose, but some of these symptoms may begin within a few hours of the last drug use. Addicts feel achy, weak, irritable, hypersensitive, and have a runny nose. Maximum withdrawal symptoms occur about 36 to 72 hours and may include a spastic jerky movement (“kicking the habit”), after the last dose. Most withdrawal symptoms reach a peak in about 5 to 6 days and usually subside over the course of two to three weeks, or sooner. Table 11.3 lists the common signs and symptoms of withdrawal from opioids.

Interestingly, there is a great deal of clinical interest in detoxification of opioid addicts, in spite of the generally held belief that withdrawal from opioids does not enhance abstinence outcome. Thus, there are several methods for detoxification.

- “Cold Turkey” is a term used to describe abstaining and going through withdrawal without any special treatment. Withdrawal in this manner is very uncomfortable, foreboding to many but not lethal. It has been used to “teach” the person not to use opioids, or to punish them for using opioids. However, no matter how severe the withdrawal, the craving for heroin remains so strong after withdrawal that heroin use will resume days after withdrawal symptoms disappear

Table 11.3 Signs and Symptoms of Opioid Withdrawal

-
- Agitation
 - Anxiety
 - Muscle and joint pain
 - Tremor
 - Insomnia
 - Runny nose (rhinorrhea, watery eyes (lacrimation))
 - Sweating (alternating chills and sweating)
 - Yawning
 - Tachycardia
 - Hypertension
 - Abdominal cramps (later stage)
 - Diarrhea (later stage)
 - Dilated Pupils (later stage)
 - Goose bumps (later stage)
 - Nausea or vomiting (later stage)
-

- Acupuncture is also effective in reducing withdrawal severity in some patients
- Medicated Withdrawal: Clonidine (Catapres), an antihypertensive medication, reduces the uncomfortable nervous system hyper excitability associated with withdrawal

Phenobarbital, a sedative, reduces overall withdrawal symptoms. Buprenorphine (an opiate receptor partial agonist, meaning its agonist effects will level off with increasing doses) has also been used to treat withdrawal. At low doses it produces less euphoria and respiratory depression than agonists like heroin or methadone but enough to cause cessation of use of other opioids without going through withdrawal.

Rapid and Ultra-Rapid Opioid Detoxification

Known by some as “instant recovery”, rapid and ultra-rapid drug detoxification (or “detox”) is controversial within the treatment community. Many treatment centers have no detox beds or units at all, but will accept chemically dependent people who have undergone detox either alone or in a hospital. Rapid detox methods are generally seen in specialized hospital settings or in high-priced (upwards of \$10,000 to \$20,000) specialty rapid detox centers, some of which advertise detox in “less than 6 hours”. Other treatment

approaches may include anesthetizing the patient for about a day and while unconscious, administering opioid antagonists (e.g., Naloxone). Such centers often have “come on” names such as “drug free at last” and “addiction no more”. The efficacy of such treatments is not without criticism or adverse side effects.

Detoxification from any drug is necessary before the guided treatment can begin. Detox occurs when the person is taken off, or chooses to stop using the depressant drug of choice (stimulant dependence does occur but is less dramatic and not life-threatening, compared to withdrawal from depressant drugs such as opioids and alcohol). Withdrawal signs upon cessation of depressant drug use are due to *physiological (physical) dependence*, caused by the adaptation of body systems to the presence of a drug over time. Generally, the longer a drug is used, and the higher the dose reached by the user, the more severe the withdrawal will be. In the case of alcohol, up to 30 percent of untreated withdrawing patients will experience delirium tremens or life-threatening withdrawal seizures. Today, such severe withdrawal effects with alcohol are rarely seen, due to pre-withdrawal treatment with other less-dependence producing medications such as clonidine or even a short-acting benzodiazepine (such as diazepam, Valium, or chlordiazepoxide, Librium). There are no rapid or ultra-rapid detox methods for alcohol dependence.

Most controversial are the methods for rapid and ultra-rapid opioid detoxification programs. Rapid protocols use an opioid antagonist such as naloxone (quick acting), naltrexone (longer acting), or the partial agonist buprenorphine (Suboxone) to cause an accelerated withdrawal, with the goal of reducing withdrawal signs and symptoms from around 8 days to about 2–3 days. In addition to an opioid antagonist, practitioners use clonidine (Catapres, a sympatholytic drug used to treat high blood pressure) and sedation to minimize acute withdrawal symptoms that can be extremely uncomfortable (but not lethal) in patients. Because withdrawal is completed more quickly, the rapid approach with appropriate medications is said to minimize relapse risk and to allow patients to enter continued treatment with naltrexone treatment more rapidly. (Unfortunately, there are almost no controlled studies that document this outcome).

Much more controversial are ultrarapid methods that use general anesthesia and complete the procedure in from one to six hours, with “no discomfort to the patient” due to a blockade of the brain’s opioid receptors from the opioid drug. Anecdotally, the patient wakes up drug-free, with no significant after effects. (Some ultrarapid detox advertisements even use the words

“opioid addiction cure”.) In spite of claims of “cure”, “safe and effective”, and “fewer relapses”, the possibility of deaths due to general anesthesia and its side effects, more relapses, and continued withdrawal symptoms after the procedure (post-acute withdrawal) make this procedure very risky. The use of buprenorphine or clonidine is as effective and has fewer risks than general anesthesia used in ultra-rapid detoxification.

Treatment After Detoxification

After detoxification, long-term treatment of opioid dependence follows one of two philosophies: total abstinence or assisted abstinence. To achieve abstinence, opioid addicts are encouraged to attend therapeutic centers or communities to learn how to live drug-free. Aids to abstinence include naltrexone (Vivitrol), an opioid antagonist that blocks the euphoric effects of opioids; and buprenorphine (Subutex, Suboxone), an opioid partial agonist that appears to reduce the craving for other opioids. Some opioid addicts are able to become permanently abstinent from all addictive drugs through these programs.

Methadone is more controversial, since some users of this “heroin substitute” continue to use the drug on a long-term basis. The best methadone programs are those in which the patient is required to take the medication in a clinic. There, urine screens are required to monitor other drug use, and patients are required to maintain an outside job and attend therapy or 12-step (Narcotics Anonymous) sessions. The intent is to wean the user off one opioid drug (usually heroin) and substitute another (methadone); maintenance on methadone may be required for the rest of their lives, because they cannot or do not commit to abstinence. “Effectiveness” of treatment in such programs is therefore not measured by an abstinence outcome, but by the quality of life achieved by the opioid-dependent patient.

Forensic Considerations

Opioids, particularly at higher than normally used doses or in opioid naïve users, produce sedation, and impairs sensory and motor skills necessary for safe motor vehicle use and related activities. The potency of some synthetic opioids, such as carfentanil, is so high that even casual contact can produce a life-threatening reaction, however, tolerance to some opioids such as

methadone is worth noting. For example, even though opioids impair psychomotor behavior, patients in medically supervised methadone maintenance programs for a few weeks are not impaired in their ability to drive. There is also evidence that patients under medical treatment with some opioids for chronic pain are not at increased risk for motor vehicle crashes. However, this should not be misinterpreted to mean that opioids do not impair driving. Initial use of opioids in non-tolerant persons or higher than normal doses in opioid tolerant individuals will produce impairment. Drivers who test positive for an opioid drug are twice as likely to cause a fatal car crash, although epidemiological data on quantitative are limited.

While drug testing for opiates is regularly relied upon in forensics, not all drug test results may reflect drug intoxication or recent drug use. Moreover, the growth of new synthetic opioids results in structurally different compounds than those detected in routine screening and confirmation methods in toxicology labs. Although a broader range of opioids can be detected, the cost for additional or expanded testing is a potential limitation in understanding causes of death or other consequences of forensic interest. Too often, the interpretation of common toxicology tests is misinterpreted. For example, standard drug screens can detect opioids in urine for about 2–4 days. However, an opioid or opioid metabolite in urine does not mean the drug has a pharmacological effect in the brain and subsequently on behavior. In such cases, only if clear bioindicators specific to opioids are also present can a reasonable scientific conclusion be drawn. Also, several reports, using a variety of analytical methods, reported detectable morphine levels in body fluids subsequent to eating poppy seeds. Additional testing was required to differentiate morphine from poppy seed eaters from opiate users. Not all opioids produce impairment of complex tasks such as driving (as in the case of methadone maintenance patients). Pharmacokinetic and pharmacodynamic drug effects should always be evaluated by properly trained and experienced subject matter experts.

Selected Bibliography

American Psychiatric Association (2022). *Diagnostic and statistical manual of mental disorders, DSM-5-TR*, 5th Edition, Washington, DC: American Psychiatric Association.

American Academy of Pediatrics Committee on Drugs (1998). Neonatal drug withdrawal. *Pediatrics*, 101(6): 1079–1088.

- Babalonia, S., Coe, M., Nuzzo, P., Lofwall, M., Ali, N., Sloan, P. Fanucchi, L. and Walsh, S. (2020). Acute administration of oxycodone, alcohol and their combination on simulated driving – preliminary outcomes in healthy adults. *Psychopharmacology (Berl)*, 238(2): 539–549.
- Baselt, R. (2004). *Disposition of toxic drugs and chemicals in man*. 7th Edition. Foster City, CA: Biomedical Publications.
- Bloom, F. E. (1983). The endorphins. A growing family of pharmacologically pertinent peptides. *Annual Review of Pharmacology and Toxicology*, 151–170.
- Cavacuiti, C. A. (2011). *Principles of addiction medicine: The essentials*. Philadelphia, PA: Lippincott Williams & Wilkins.
- Center for Disease Control and Prevention (2016). Increases in drug and opioid overdose deaths – United States 2000–2014. 64(50): 1378–1382.
- Concheiro, M., Chessier, R., Parti, J. and Cooper, G. (2018). Postmortem toxicology of new synthetic opioids. *Frontiers in Pharmacology*, 9: Article 1210.
- Drug Overdose Death Rates. National Institute on Drug Abuse. Trends & Statistics. 9 February 2023. Retrieved March 2023.
- Fritschi, G. and Prescott, W. (1985). Morphine levels in urine subsequent to poppy seed consumption. *Forensic Science International*, 27(2): 111–117.
- Gerostamoulos, D. (2009). Opioids. In: *Wiley encyclopedia of forensic science*, Jamieson, A. and Moenssens, A. (Eds), Chichester, UK: John Wiley & Sons Ltd.
- Jaffe, J. and Martin, W. (1975). Narcotic analgesics and antagonists. In: L. Goodman and A. Gilman (Eds), *Pharmacological basis of therapeutics*. New York: Macmillan, pp. 245–283.
- Levine, B. (2010). *Principles of forensic toxicology*. AACC Press
- McHugh, P. and Kreek, M. (2008). The medical consequences of opiate abuse and addiction and methadone pharmacotherapy. In: J. Brick (Ed.), *Handbook of the medical consequences of alcohol and drug abuse*. Taylor and Francis Publishing, pp. 303–339.
- Moskowitz, H. and Ogden, E. (2004). Effects of alcohol and other drugs on driver performance. *Traffic Injury Prevention*, 5: 185–195.
- O'Donnell, J., Gladden, M., Mattson, C. and Kariisa, M. (2018). *Morbidity and Mortality Weekly Report*, CDC 67(27): 767–768.
- Resine, T. and Pasternak, G. (1996). Opioid analgesics and antagonists. In: *Goodman and Gilman's the pharmacological basis of therapeutics*, 9th Edition (J. G. Hardman and L. E. Limbird (Editors-in Chief)), McGraw Hill Publishing Company, pp. 521–556.
- Shenoy, S. S. and Lui, F. (2022). *Biochemistry, endogenous opioids*. National Library of Medicine: StatPearls Publishing, Bookshelf ID NBK532899 PMID 30422494
- Statista.com (2023). *Share of global fentanyl consumption 2018–2021 by country*.
- Stout, P. R. and Farrell, L. J. (2002). Opioids – Effects on human performance and behavior. *Forensic Science Review*, 15(1): 30–59.
- Swonger, A. and Constantine, L. (1983). *Drugs and therapy*. Boston: Little, Brown.
- Ujváry, I., Jorge, R., Christie, R., Le Ruez, T., Danielsson, H. V., Kronstrand, R., Elliott, S., Gallegos, A., Sedefov, R. and Evans-Brown, M. (2017). Acryloylfentanyl,

- a recently emerged new psychoactive substance: A comprehensive review. *Forensic Toxicology*, 35: 232–243. DOI: 10.1007/s11419-017-0367-8
- UNODC (2017). Recommended Methods for the Identification and Analysis of Fentanyl and Its Analogues in Biological Specimens (Vienna).
- US Drug Enforcement Administration (2017). *Drugs of abuse*, 2017 Edition.
- U.S. National Library of Medicine National Center for Biotechnology Information. Open Chemistry Database (2017).
- Verster, J. C., Veldhuijzen, D. S. and Volkerts, E. R. (2006). Effects of an opioid (oxycodone/paracetamol) and an NSAID (bromfenac) on driving ability, memory functioning, psychomotor performance, pupil size and mood. *Clinical Journal of Pain*, 22(5): 499–504.

Inhalants: A Matter of Life and Breath!

12

Caution: the following chapter will tell kids how to inhale these mind-altering chemicals! But kids, do so only if you want a quick way to die or suffer severe neurocognitive damage. This class of chemicals is the most dangerous of all the ones discussed in this book. The reasons that anyone would use these chemicals are as varied as peoples' expectations in life. The reason for discussing inhalants at all is to educate parents about what they are, what they do and don't do, and how young people, the primary users, can be seriously damaged or killed by these chemicals. Such education is currently the only way we have to reduce the danger of inhalants to society.

What Are Inhalants?

An inhalant is any volatile chemical solvent that can enter the body through inhalation (hence the name). Inhalants that are used illegally come in many forms and unlike most other problem use drugs can be easily found in the home or local hardware store. There are four major categories of inhalants: volatile solvents (e.g., liquids that vaporize at room temperature such as paint thinners, cleaning products, gasoline, glues, correction fluids and felt-tip markers), aerosols, (e.g., spray paints, hair sprays, fabric protector sprays), gases (e.g., medical anesthetics such as chloroform, halothane, nitrous oxide used by dentists but also found in whipped cream cans, butane lighters and other aerosol products) and nitrites. Nitrites is a special class of inhalants found in some cleaners, room odorizers and other cleaners even though they

Table 12.1 Commonly Used Inhalants

Chemical Inhalants	Sources
Toluene	Acrylic paint, airplane glue
Fluorocarbons, difluoroethane (Freon 152a)	Aerosol propellant (e.g., keyboard cleaners)
Chloroform, nitrous oxide	Anesthetics
Bromochlorodifluoromethane	Fire-extinguishing agent
Propane, butane	Fuel, lighter fluid, torches
Hydrocarbons, tetraethyl lead	Gasoline
Benzene, carbon tetrachloride, methylethyl ketone, <i>n</i> -hexane, toluene, trichloroethylene, trichloroethane, xylene	Glues, plastic cement, rubber cement
Toluene, xylene	Inks
Methylene chloride	Paint strippers/thinners
Trichloroethylene, toluene	Paints, varnishes, lacquer
Fluorocarbons	Refrigerants
Amyl nitrites	Room odorizers
Chlorinated hydrocarbons, toluene	Shoe polish
Trichloroethane, trichloroethylene, carbon tetrachloride	Spot remover
Tetrachloroethylene, trichloroethane, trichloroethene	Typewriter correction fluid

Source: Modified from Krolecki and Shih (2008)

are prohibited by the Consumer Product Safety Commission in the US). Their primary effect is dilation and relaxation of blood vessels. Table 12.1 lists some of the more common inhalants and their sources.

History of Inhalant Problem Use

Awareness of mind-altering effects of inhalants goes back at least to the ancient Greeks, who used inhalants as part of a rite of passage for their youth. In the US (1940s), ether and nitrous oxide were used in public laughing gas demonstrations, followed by gasoline sniffing in the 1950s and glue sniffing in the 1960s. In 2022, inhaling or “chroming” has become popular again. It is estimated that 3.6 percent of 8th graders, 2.4 percent of 10th graders and 1.8 percent of 12th graders reported using inhalants in the last 12 months. Compared with other intoxicants, gasoline, glue, and other inhalants are easy to obtain and inexpensive and unfortunately very dangerous.

Administration, Absorption and Distribution

Inhalants, by their very nature, are administered through the pulmonary system. There are four basic techniques of inhalant administration: “huffing”, in which a cloth is saturated with the solvent (e.g., gasoline) and placed near the face and the fumes inhaled; “bagging” in which the solvent (e.g., airplane glue) is placed into a paper bag and the user cups the open end of the bag around their nose and mouth and inhales; “snorting” in which a small container with solvent (e.g., butane canister) is inserted into a nostril, the other nostril is held closed and the subject inhales quickly; and “ballooning” in which the intoxicant (e.g., nitrous oxide) is transferred into and inhaled from a balloon. “Chroming”, which gets its name from inhaling chrome-based paints is the latest iteration of this dangerous high.

Because the pulmonary route brings the drug directly into the circulation, blood concentrations of inhalants increase very rapidly (10–20 seconds). Similarly, most inhalants remain in the circulation for a relatively short time because they are expired from the lungs (like cigarette smoke) or rapidly metabolized. Even though administration, distribution, and elimination are rapid in comparison to many other drugs, the effects of inhalants may continue after the concentration of the drug in blood drops to relatively low amounts.

Identifying Inhalant Abuse

Identifying acute abuse (i.e., being under the influence of an inhalant) is not difficult (see next section) but the duration of these effects is short lived. Parents and others should be alert to chemical odors on breath or clothing, paint or other stains on the hands, clothing and around the mouth/face, hidden cans of spray paint, chemical-soaked rags or towels, etc.

Biobehavioral Effects of Inhalant Use

Inhalants produce very rapid changes in cognitive and psychomotor abilities, as summarized in Table 12.2. Other significant clinical indicators of inhalant use may include belligerence, assaultiveness, apathy, impaired judgment, and impaired social or occupational functioning during or shortly after use.

Table 12.2 Biobehavioral Effects of Inhalants

<ul style="list-style-type: none">• Drowsiness and relaxation• Lethargy• Sedation and deep sleep (unconsciousness)• Hallucinations (auditory and visual)• Hypoxia• Euphoria and excitation• Agitation, belligerence, apathy, impaired functioning• Seizures• Ataxia or incoordination• Headache• Dizziness• Nystagmus• Slurred speech• Tremor• Blurred vision

Table 12.3 Signs and Symptoms of Inhalant Withdrawal

<ul style="list-style-type: none">• Sleep disturbances• Tremor• Irritability• Sweating• Nausea• “Fleeting illusions”

Tolerance and Dependence

Tolerance to the effects of inhalants has been reported but is usually limited to individuals with heavy use. However, the prevalence and significance of tolerance is generally not known.

Most dependence criteria that apply to other drugs do not apply to inhalants. However, there are reports of a withdrawal syndrome 2–4 days after use (see Table 12.3 for withdrawal symptoms).

The withdrawal syndrome is not well documented, its meaning is not known, and it occurs in only a small percentage of individuals using inhalants. Whereas the diagnostic manuals do not indicate that inhalants can cause chemical dependence (“addiction”), one set of studies has set the incidence of addiction at 4 percent of users.

Medical Consequences of Inhalant Use

Inhalants can cause death from anoxia (lack of oxygen), respiratory depression, cardiac arrhythmia, inhibition of nervous system signaling to the heart (vagal inhibition) and rapid onset pulmonary edema (congestion of the lungs). Effects vary with acute (short term) or chronic (long term) exposure and specific inhalant type. The most common toxic medical effects are listed in Table 12.4.

Prenatal Effects

All medications have the potential to alter cell growth in the fetus during development, particularly during the early stages of pregnancy. Chroming is more popular with children who are less likely to be pregnant than older persons. At this time, there are insufficient data on the relationship between inhalant medications and fetal development but the major medical consequences (Table 12.4) on the mother are almost certain to have harmful effects on a fetus.

Table 12.4 Major Medical Consequences of Inhalant Use

Hematologic (blood)	Abnormalities in oxygen-carrying hemoglobin that blocks oxygen binding; vasodilation and increased intracranial pressure; increases in carbon monoxide binding to hemoglobin; metabolic acidosis (chronic use); rhabdomyolysis (muscles break down)
Cardiac (heart)	Cardiac arrhythmias; sensitization of cardiac receptors may lead to sudden death when stress-released catecholamines over-stimulate the heart
Central nervous system (brain and spinal cord)	Chronic use is associated with cerebral and peripheral neuropathies, and cognitive impairment. Acute intoxication (see Table 12.2)
Hepatic (liver)	Hepatic necrosis (liver cell death), which may be secondary to toxic metabolites of the inhalant
Pulmonary (lungs)	Oxygen displacement, hypoxia, asphyxiation, congestion and suffocation
Other Consequences	Asphyxiation, convulsions, seizures, coma, death

Forensic Considerations

Although inhalant use disorders have acute and chronic effects, including death that may be of forensic interest, the study of inhalants in crimes and accidents is difficult. Inhalants have a very short half-life and are rapidly eliminated from the blood. Unless a blood sample is obtained shortly after an incident, it is unlikely that any inhalant will be detected. In fact, this may explain why the reported incidence of inhalants involved in motor vehicle crashes or DWI arrests is relatively low compared with other drugs. Little is known about how lingering toxic effects of inhalants may affect behavior that would affect driving, decision-making, appreciation of consequences, or other acts of forensic interest. Pharmacokinetic and pharmacodynamic drug effects should always be evaluated on a case-by-case basis.

Selected Bibliography

- American Psychological Association, Diagnostic and statistical manual of mental disorders, DSM-V-TR, 5th Edition, Washington, DC, American Psychiatric Association, 2022.
- American Psychiatric Association (2000). *Diagnostic and statistical manual of mental disorders* (4th Edition, text revision: DSM-IV-TR). Washington, DC: American Psychiatric Association.
- Garriott, J. and Petty, C. (1980). Death from inhalant abuse: Toxicological and pathological evaluation of 34 cases. *Clinical Toxicology*, May 16(3): 305–315.
- Johnston, L. D., O'Malley, P. M., Bachman, J. G. and Schulenberg, J. E. (2011). *Monitoring the future national survey results on drug use, 1975–2010: Volume I, Secondary school students*. Ann Arbor: Institute for Social Research, The University of Michigan.
- Kolecki, P. and Shih, R. (2008). Inhalant abuse. In: Brick, J. (Ed.), *Handbook of the medical consequences of alcohol and drug abuse*. Taylor and Francis Publishing Co. pp. 367–384.

Marijuana: The Sometimes Illegal Recreational Plant

In 1936, a movie titled Reefer Madness was produced to frighten youth by exaggerating the effects of marijuana use and for many decades cannabinoids were without exception illegal in The United States and many other countries. In the last ten years, marijuana use has been decriminalized in many parts of the United States and Europe and the medical use of cannabinoids has become legal and cannabis dispensaries have become a multi-billion-dollar industry. Although rarely lethal and far less toxic to humans than alcohol or nicotine, widespread legalization of cannabis is problematic. As restrictions on the sale of marijuana have decreased, users seeking treatment have increased as have motor vehicle accidents related to the use of this drug. The trend appears to be to decrease penalties for use and increase availability of marijuana products. While the use of cannabinoids in psychiatry and medicine holds some promise, ongoing scientific evidence about the harmful consequences of this drug continues to accumulate.

What Is Marijuana?

Early humans were primarily hunter-gatherers living in small often nomadic groups until about 10,000 years ago when farming took root in Asia and eventually spread throughout the world. As agriculture grew, larger societies formed and economies based on agriculture flourished, marking the start of modern civilization. Throughout history plants have provided humans with a variety of benefits. In addition to being a source of oxygen, food, fiber,

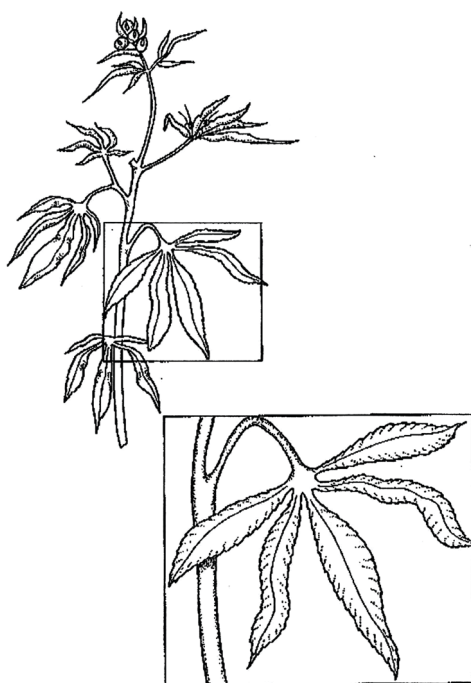


Figure 13.1 Cannabis plant

shelter, and herbal and other medicines, some plants are consumed because they contain psychoactive compounds. One such plant is cannabis. In this country, the term “marijuana” is used to describe the whole plant or any part of it. A typical plant is illustrated in Figure 13.1.

Cannabis can be identified by its leaves which come in various shapes (long, short, thin, elliptical) and colors but all have an odd number (e.g., 3, 5, 7) of variegated leaves. Some varieties, such as *Cannabis indica*, rarely grow more than four to five feet tall, whereas *Cannabis sativa* can reach heights of 15 feet or more. There are dozens of hybrids of the plant cultivated to achieve desired characteristics in a growing horticultural industry. Hemp is another name for cannabis sativa. They are two versions of the same species but vary significantly in their psychoactive effects.

The conditions that allowed agriculture to thrive in Asia were most likely conducive to cannabis as well but different species grow wild or are cultivated for various uses in many different regions of the world. In fact, George Washington grew *Cannabis sativa* on his farm in Mount Vernon, probably to make hemp rope (an important commodity for sailing ships in that era).

Since the weed grows well in moderate climates, it spreads readily and is now wild throughout many portions of the United States. Today (2024), marijuana horticulture coupled with the sale of cannabinoid products is a \$35 billion per year industry, making it one of the largest cash crop industries in The United States and other countries. That figure is expected to reach \$55 billion dollars by about 2026. That does not include state or federal tax revenue or sales from cannabinoid products, such as CBD.

Different Types of Marijuana-Based Products

There are different species of the cannabis plant, including hybrids designed to have high THC content. Marijuana is called many different names depending on geographical and cultural factors. The origin of street names for marijuana, such as grass, Maryjane, weed, pot, and tea (and many others) have no direct bearing on the product but allowed reference to the drug in conversation without referring to an illegal drug. With legalization of the sale of marijuana in many places, such covert language is less common and the country of origin is often used to describe the product. Prior to hybrid horticultured products, marijuana often came in different colors (e.g., goldish, reddish, black, greenish-brown) that resulted when farmers sheared the roots on one side of the plant with a shovel a few days before harvest producing products with names like Acapulco or Colombian gold. This root shearing cuts off about half of the roots and interrupts the supply of plant hormones that prevent discoloration. By interrupting the supply of plant hormone, chlorophyll breaks down and the plant takes on a golden color. “Punta Roja” appears red naturally, whereas other plants appear black because the cells of the harvested plant are squashed (the plant is run through the rollers of an old-fashioned wringer washing machine or similar device) and left to ferment like black tea.

With continued legalization, potency and cultivation of the plant varies. Although different variations of the plant exist (leading to the incorrect conclusions there were several species of cannabis) the basic product of the dried vegetation has not changed in appearance. The most common marijuana colors are shades of greenish-brown. Today, color has little to do with actual potency, despite marketing efforts to convince buyers otherwise. Some hybrids have a higher content of the most psychoactive ingredient and are very potent. The plant components that make up marijuana vary considerably, but generally the entire plant is dried, milled like tobacco and smoked. Some users will only smoke the unpollinated bud of the female plant (Sinsemilla)

that has the highest THC content; the remainder of the plant (called “shake”) is considered not worth smoking. With the trend towards more wide-spread legalization, it is probably just a matter of time before marijuana becomes genetically modified or cultivated to be more uniform in appearance and identified by quantified THC content labels to make consumers more informed about their purchase. Marijuana is typically sold by the ounce on the street or at retail establishments.

Hashish is relatively pure and is made by scraping the resin from the plant. Hashish also comes in different colors and textures. These range from golden blocks that crumble into fine powder, to dark, dense, oily blocks. Hashish is usually smoked in a small pipe, but it is occasionally eaten (e.g., “hash” brownies or cookies). Hashish is sold in chunks that are fractions of an ounce or kilogram. As a product, hashish is easier to transport (smuggle) and pound for pound, more profitable than marijuana. With legalization of the sale and cultivation of marijuana in many places, the economic advantage of selling hash has diminished.

History of Marijuana Use

The psychoactive properties of cannabis have been known for nearly 5,000 years, with the earliest reference dating back to the Shen Nung dynasty in China, circa 2737 BC. Some historians opine the cultivation of cannabis fiber (for clothing and rope) and oils (for medicinal and other uses) are reportedly much earlier. Like other organic drugs (e.g., opium, cocaine), cannabis was used to treat a wide range of ailments including “female weakness”, rheumatism, malaria, beriberi, constipation and absent-mindedness. When mixed with wine it was used as an anesthetic. By the year 1000 AD cannabis had reached northern Africa, where its reputation and use flourished. By 1830, an Irish surgeon began experimenting with cannabis as a muscle relaxant, anti-convulsant and analgesic.

Historically, the most common legal form of cannabis is from hemp, used in the manufacture of rope and birdseed. Hemp and cannabis seeds used in birdseed contain very little of the active ingredient (THC). The active ingredient in cannabis has been used to treat certain medical ailments such as glaucoma (increased pressure in the eye), and to treat some of the side effects (e.g., nausea) associated with cancer chemotherapy. Some of the more common products of the cannabis plant are shown in Figure 13.2.

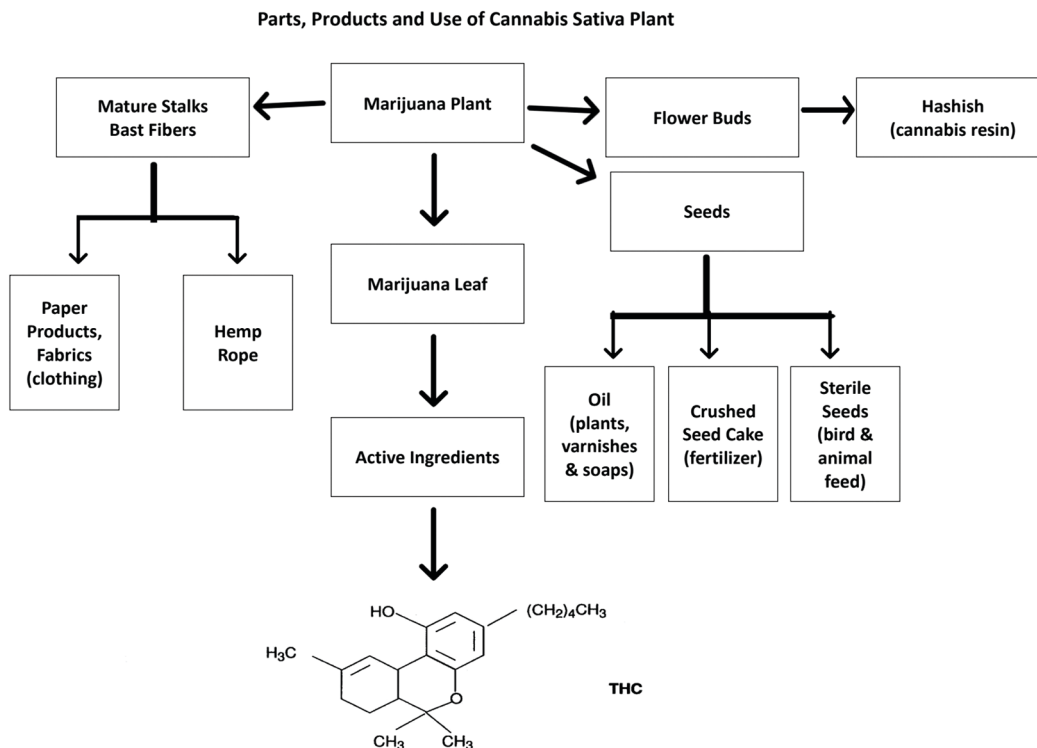


Figure 13.2 The cannabis plant is used in the manufacture of many legal products. Compounds such as delta-9-tetrahydrocannabinol (shown) or cannabidiol are primarily responsible for the psychoactive effects of marijuana and hashish, respectively (Adapted from Phillips, 1985)

Who Uses Marijuana?

Cannabis has always had a certain mystery associated with its use. Part of the intrigue comes from legends from the Mediterranean area about the use of hashish by a religious cult called the Hashishiyya. The Hashishiyya murdered political enemies for their leader, Hasan-Ibn-Sabbah, from whose name the term assassin is probably derived. By the middle of the 1800s, the use of hashish had spread through Europe and appears in such literary works as *The Count of Monte Cristo* (Dumas), *Le Club Hachischins* (Gautier) and *Artificial Paradise* (Baudelaire). The descriptions of hashish intoxication found in these works are quite accurate and make for very interesting reading.

The use of marijuana and hashish increased dramatically during the 1950s and 1960s when a large portion of our society “turned on, tuned in and dropped out”. As public interest and concern grew, social scientists began monitoring drug use through detailed, anonymous questionnaire surveys. The target population for many of these studies was high school students. Based on the results of large scale, nationally distributed surveys, it appears that regular use of this drug was quite common. In 2020 marijuana use had increased in comparison to use 20 years ago. Today, about 13.2 percent of children aged 12–17 reported having used marijuana and 5.8 percent reported use within the last month of the survey. Among 12th graders, 31 percent have smoked marijuana within the last 12 months. Among adults, age 18 or older, 49 percent admitted to marijuana use and almost 14 percent admitted use within the last month.

Another factor that influences use is availability. Although improved law enforcement techniques make successful smuggling of this bulky product hazardous for smugglers, in the United States decreased funding and support for Border Control agencies to intercept drugs entering the southern border coupled with decreased legal penalties and increased legalization of marijuana, can only increase availability and subsequent use.

What Is THC?

Cannabis contains a psychoactive substance called delta-9-tetrahydrocannabinol (delta-9-THC) or simply “THC”. Most illicit use of cannabis is related to the psychoactive effects of THC. One species of the plant, *Cannabis indica*, has a relatively high concentration of THC, harsh taste, is quite hearty, and

will grow in most areas where other weeds can survive. The other major species, *Cannabis sativa*, has relatively low concentrations of THC, a smooth taste, and does not grow well in colder climates. Marijuana cultivators have experimented with hybrids to obtain the best of both species. The cultivation, showing, and sale of this plant have become a cult-like cottage industry in recent years. In general, the concentration of THC in street-purchased marijuana has increased from about 0.5 to 2 percent in the 1970s to as high as about 10 percent in the 1990s. Today varieties of marijuana can be found containing 3–22 percent THC.

THC is found in the sap like resin of the cannabis plant (Figure 13.2). The greatest concentration of THC is found in the flowering tops of the plant, with less in the leaf and stalk. This drug can be prepared in different ways depending upon the part of the plant used. For example, in India, charas (known also as hashish, or “hash”) is made from a pure form of the resin, which is carefully removed from the flower, leaf and plant stem. Sinsemilla comes from the seedless bud of the female plant and ganja is made from the dried flower tops of the female plant. Bhang is prepared from the dried leaf and stem powder and is usually served in a drink or as candy.

What is CBD?

Cannabidiol (CBD) has become a popular profitable and legal compound derived from the hemp plant. It is not psychoactive and does not cause dependency. While any drug in sufficient quantities can be toxic, the dose of CBD for a toxic overdose is so high that it is not of concern under typical treatment applications. For example, in a 165-pound person, a dose of just over 18,000 mg taken in a short period would be potentially fatal, as compared with a typical daily dose of 100 mg dose of CBD oil. Nevertheless, reported side effects include nausea, fatigue, insomnia, dizziness and use of CBD may have pharmacokinetic interactions with other medications because its metabolism competes with that of other medications. If you are taking any medications, check with your physician about using CBD. Although marijuana (THC) is classified as a Schedule 1 drug, hemp extract from marijuana is not a controlled substance because it contains less than 0.03 percent THC.

CBD is available as an oil, lotion, tea or in edible form (e.g., CBD gummies) and is widely available at dispensaries and other stores and advertised to self-treat a variety of ailments. Research on the benefits of CBD shows

some promise in treating anxiety, insomnia and pre-clinical and in-vitro studies suggest CBD may have some value in treating other mental illnesses, including Alzheimer's. However, these findings are not robust and the efficacy and safety of CBD in treating the plethora of ailments described is yet to be determined.

What are Synthetic Cannabinoids?

Synthetic cannabinoids such as K2/Spice are man-made and not a natural drug. Legal definitions of what constitutes a drug are based on specific molecular characteristics.

As an effort to circumvent legal definitions, some entities have explored the psychoactive properties of drugs slightly altered to allow them to produce psychoactive effects but enough to not be included in the net of legal definitions. There are hundreds of synthetic cannabinoids in the world market that have minor structural changes that do not result in pharmacological changes but are "legal" alternatives to the illegal drug. Synthetic cannabinoids can cause a variety of behavioral (e.g., agitation, confusion, incoordination, hallucinations) and medical (e.g., tachycardia, tachypnea, hypertension) observable or detectable consequences. However, most common toxicology screens for THC do not detect synthetic cannabinoids.

How Is Marijuana Administered?

The most common route of administration is through the pulmonary system, although the plant can be ingested and absorbed through the gastrointestinal system as well. Most marijuana is milled and smoked like tobacco in a pipe or in hand-rolled cigarettes often called "joints", "blunts", or "bones", because of their appearance. Usually, the dried plant leaf is smoked. The stem and seeds may also be smoked, but they are not nearly as potent as the leaf. When smoked, THC enters the circulation as an airborne particle and is rapidly distributed into the blood. The blood carries THC to various tissues, including the brain. Definite effects are noticeable to the smoker within several minutes. THC may be taken orally as well (in brownies, for example); however, the amount of drug required to produce psychoactive effects is approximately two to three times more than when it is smoked. This difference is probably

due to bioavailability (more drug enters the blood through the lungs than through the gastrointestinal tract).

Distribution and Elimination

When smoked, THC enters the circulation almost immediately, reaching very high blood levels within five to ten minutes. Although the psychoactive effects begin within minutes, the relationship between reports of being “highest” and peak blood level is not as highly correlated as for some other drugs. The greatest subjective high usually occurs after peak concentrations in blood are reached; in some studies, this occurs roughly 15 to 45 minutes after smoking. This may be, in part, due to metabolism, which occurs primarily in the liver since the high is produced by a combination of THC and one of its active metabolites. Since the metabolite 11-hydroxy-delta-9-THC has effects nearly identical to the parent compound, it is possible that both compounds combine in an additive fashion. Thus, it may take some additional time after peak THC levels in blood for metabolites to form and the subjective high to be reached. However, empirical evidence to support this notion is lacking. There are fairly large differences among (1) how individuals feel, (2) drug potency and (3) average doses. The influence of “set” (the expectation of the user) and “setting” (the environment in which the drug is used) is also quite important with marijuana. The high from a single joint usually lasts up to about two hours, but residual effects can last longer.

Neuropharmacology of Cannabinoids

All compounds derived from the cannabis plant or THC or its metabolites are referred to as cannabinoids. The discovery of cannabinoid (CB) receptors is probably the most exciting finding relating to marijuana pharmacology within the past 30 years. CB receptors are a class of cell membrane receptors called G-protein receptors. There are two known subtypes, CB1, which are found primarily in the brain (but also in the lungs, liver and kidneys); and CB2, which are found mainly in the immune system and in blood-producing cells. THC binds to the CB1 receptors whereas CBD binds mostly to CB2 receptors and therefore has no psychoactive effect (i.e., it does not make you high).

In general, the various effects of cannabinoids working on these receptors cause the multitude of effects seen when individuals use this drug. Of particular importance to a marijuana user are the effects on the brain – calming, anxiety reducing, appetite-enhancing and other intoxicating actions. Cannabis (and the naturally-occurring endocannabinoids) produces many biobehavioral effects produced by mood-altering drugs and their naturally-occurring brain chemicals that keep the brain in balance.

There are more than 500 different chemicals in the marijuana plant, including over 100 cannabinoids. These are the pharmacologically active substances in marijuana and other products of the cannabis plant. Of the major cannabinoids, the most psychoactive is delta-9-tetrahydrocannabinol (D-9-THC), whose structure is illustrated at the bottom of Figure 13.2. In hashish, the primary psychoactive compound is a structurally related compound, cannabidiol (CBD). In addition to D-9-THC, metabolites or breakdown products of this compound, such as 11-hydroxy-D-9 THC, are also psychoactive. Thus, unlike many drugs, the metabolism of D-9-THC by liver enzymes does not decrease intoxication, it prolongs it. Other common cannabinoids are CBD, D-8-THC, tetrahydrocannabivarin (THCV), cannabigerol (CBG). None of these cannabinoids have been approved by the U.S. Food and Drug Administration nor have they been rigorously researched. The one exception is an FDA approved CBD product, Epidiolex that is used to treat two rare forms of epilepsy.

Given the range of biobehavioral effects from cannabinoids, it should not be surprising to learn that their molecular receptors are distributed most densely throughout the cerebellum, basal ganglia, and hippocampus of the brain. These areas allow movement, emotions and memory. THC inhibits the activity of adenylyl cyclase, an enzyme that stimulates cAMP to alter the excitability of the neuron. The greater the psychoactive effect of the drug, the greater the inhibition of the enzyme.

Interestingly, there are about a hundred times as many cannabinoid receptors as opiate receptors in the brain. One might wonder why the brain has so many receptors for any cannabinoids. The answer should be obvious – the brain must manufacture an endogenous compound with properties similar to THC. The brain does in fact contain a naturally present molecule called anandamide, which is one of several “endocannabinoids” that bind to the CB receptors. Current research is designed to determine whether endocannabinoids mimic all the actions of cannabis at its receptors in the brain.

Biobehavioral Effects of Marijuana

General Effects

Any discussion of the general effects of marijuana should begin with a disclaimer: marijuana is one of the least studied drugs in the laboratory and more large scale controlled clinical studies are still needed. There are several reasons why marijuana is so under-researched: 1) being a natural product that is smoked or ingested by humans, it is difficult to replicate human marijuana use in animal studies, 2) street doses and concentrations of the drug taken by individuals vary tremendously and are difficult to replicate in controlled studies, 3) laboratory research is difficult because marijuana (THC) is a Schedule I DEA drug, which makes experimental quantities difficult to obtain due to excessive paperwork and limited quantities of the substance, and 4) a lack of strong unequivocal scientific literature makes grant proposals weaker in background support as compared to purer, easier to obtain drugs such as cocaine, heroin, alcohol and so on. This makes approval and funding of marijuana research proposals more difficult, since the scientific quality of such proposals tends to be more suspect. Because of the relative lack of research on marijuana, there are major differences in interpretation of clinical effects that one will find when looking for accurate information in the scientific literature or online. Particularly striking are the varied speculative opinions of “experts” on the Internet regarding the effects of marijuana. For the reader seeking accurate information, it is best to focus on mainline respected websites such as those of the National Institutes of Health, academic research centers, mainstream peer-reviewed journal and nonprofit organizations that appear to lack bias about the effects of marijuana and not articles written by purveyors of cannabinoid products and internet bloggers not associated with readily identified authorities (e.g., NIDA).

Marijuana users describe the effects of the drug along different dimensions. Not all effects are experienced simultaneously, or in every user each time they administer the drug. Some of the more consistently reported effects are described in Table 13.1.

Most people who smoke marijuana believe that marijuana enhances pleasurable things even more. Users report that sex is much more physically enjoyable because of enhanced tactile sensations. This effect has been offered as evidence that marijuana use increases promiscuity in women or rape in men, but the scientific evidence that there is a causal relationship is slim. At best,

Table 13.1 Common Subjective Effects of Marijuana Intoxication*

<ul style="list-style-type: none">• Feeling relaxed• Thirsty (may be related to dry or “cotton” mouth)• Food cravings (“munchies”)• Touch and other sensations (e.g., taste, sounds) enhanced• Colors appear more vibrant• Euphoria• Metaphysical thoughts• Time distortion (sense that time slows down)• Bouts of spontaneous laughter (common events seem funny)• Memory impairment
--

*Intoxication begins within minutes of smoking.
Subjective effects are greatest shortly after use but may last up to 2 hours.

it may suggest that people who use marijuana are part of a subculture that has more liberal attitudes toward sex. There is no scientific evidence that marijuana leads to such behavior. Use of marijuana is usually associated with feelings of relaxation and decreased tension, not violence.

After smoking a joint, most marijuana users report dry (“cotton”) mouth and an increase in appetite, especially for snack foods. Interestingly, the “munchies” are not associated with changes in blood glucose, which normally stimulate hunger.

Marijuana has so many pharmacological and biobehavioral actions that it is classified separately from other drugs. The drug is sometimes described as a hallucinogen; however, it rarely produces frank hallucinations, except at extremely high doses. Marijuana users tend to consume low doses of the drug so that they do not experience true hallucinations, although differences in tolerance, experience, and drug potency may lead to unexpected and undesired toxic effects.

Communication, Memory, Driving and Motivation

Many undesirable side effects are associated with marijuana use. The most common is the false sense of enhanced creativity and ability to communicate. In a social environment where the perception of enhanced abilities may have few significant consequences, such effects are relatively benign. However, in a working or learning environment where the decisions made by an intoxicated person or the actual quality of their material work may affect the individual or group, such effects may be quite harmful.

Short-term memory is greatly impaired by marijuana use. This may result in a deterioration of goal-directed behavior, particularly when the user must go through several steps to successfully complete a task. In a social setting, a short-term memory lapse that leads you to forget what you were about to do or say may appear quite humorous and may actually be part of the desired high. At the workplace, at home, in school, or elsewhere, such psychoactive effects are obviously harmful. In other situations, such as driving a motor vehicle, these effects may be dangerous.

Most field research on motor vehicle accidents makes it difficult to single out marijuana intoxication as the primary cause of an accident because most of the drivers were drinking alcohol as well. Therefore, alcohol intoxication may have been listed as the only cause of the accident. Controlled field studies also indicate that marijuana decreases risk-taking while driving (e.g., fewer unsafe passes, decreased speed). However, the contribution of marijuana intoxication cannot be ignored when one considers how important memory is to safe driving and that marijuana impairs memory. Consider the following, for example. To safely exit from a highway requires several steps, including remembering what exit you want, remaining vigilant for the exit, signaling your intention to change lanes, checking your mirror and blind spots for other cars, executing a lane change and slowing down to exit ramp speed. Forgetting to do any of these steps can result in an accident.

Subjects driving experimental vehicles while under the influence of marijuana responded fairly well to emergency situations when they were given advance notice that they must respond. However, when there was no warning of the emergency response, subjects under the influence of marijuana were impaired in their ability to make emergency decisions. Although research shows that marijuana use increases the relative risk for an accident, field studies of marijuana's effects on driving must be interpreted carefully for the following reasons: 1) in many cases other drugs (e.g., alcohol) are present in such high concentrations that they could account for any impairment 2) driving; unlike alcohol, THC can be detected long after its effects have dissipated; 3) many studies correlate behavior (e.g., an accident) with the presence of an inactive metabolite of THC (9-carboxy-THC), not with THC itself; negative findings may be related to how long ago the drug was used. Even so, when these factors are considered, it is clear that THC impairs driving skills in a dose dependent manner.

Synthetic cannabinoids (K2/Spice) are manufactured in the lab and sprayed on dry or cut plant material so it can be smoked in a joint or vaporized and

ingested by e-cigarette or similar devices. Synthetic cannabinoids are not safe and may have even more harmful and unpredictable effects as compared with marijuana. Unfortunately, clever and attractive marketing of this product is effective in contributing to their use by young people. Although similar in structure to THC, the pharmacological actions of these are not fully understood but the effects are similar to that of THC. The harmful effects of K2/Spice include impaired driving (failure to maintain position, falling asleep while driving, altered perception) related psychomotor impairments.

Strength, Coordination and Judgment

In the laboratory, very low doses of THC have been shown to have little effect on the performance of motor tasks and reaction time. However, at commonly used doses, THC has profound deleterious effects. Laboratory studies have shown that the ability to drive a car or fly an airplane is seriously impaired by one to two joints due to decreases in muscular strength, coordination, judgment, and perception of time and distance. Of particular concern is that impairment usually lasts longer than the subjective high produced by the drug.

There have been many reports that chronic marijuana use leads to apathy and loss of interest in accomplishments, slow thinking, and other cognitive impairments. Unfortunately, these reports failed to determine whether such cognitive impairments existed prior to chronic marijuana use or were directly related to the use of the drug. Objective scientific evidence for “amotivational syndrome” produced by chronic marijuana use is still lacking. Even so, marijuana intoxication impairs basic cognitive processes such as memory and distorts perception. To the extent that these are the foundations of learning and motivation, chronic marijuana use is harmful. Poor learning usually results in poor performance, and poor performance can be a disincentive to future learning. Thus, a cascading loop of failure can develop. Additional research is needed to study the effects of long-term moderate and heavy use of this drug on psychological and physiological processes.

Medical Uses

THC does have several potential medical uses even though at the time of this publication, the U.S. Drug Enforcement Agency (DEA) lists it as a Schedule I Drug. Schedule I drugs have no current accepted medical use by DEA

definitions. Nevertheless, as a bronchodilator, THC may be useful in the treatment of asthma, particularly when other medications are not effective. However, under such circumstances, the drug would probably best be administered orally, rather than through the pulmonary system, since particles in smoke would irritate sensitive lung tissue and exacerbate the asthma. Long-term use of THC as an antiasthmatic may be contraindicated since there is also evidence that chronic use of marijuana results in bronchoconstriction.

THC is also effective in treating glaucoma. Glaucoma is a disease characterized by increased intraocular pressure and is the second leading cause of blindness in the United States. Eventually, the pressure within the eyeball increases to the point that the optic nerve, which sends information from the eye to the brain, is damaged. Clinical case studies suggest that marijuana may cause a dose-dependent decrease in intraocular pressure, lasting for several hours. Although the use of marijuana will not cure glaucoma, it can slow down the progressive loss of vision. Inhalation, oral consumption, or intravenous injections of THC are about equally effective in treating glaucoma, whereas topical administration (e.g., eye drops) is not. The psychoactive effects associated with THC treatment may not be well tolerated by some patients.

The medical use of THC in treating nausea and vomiting associated with chemotherapy is probably the most accepted medical use of THC. Dronabinol, a THC drug, has been found to be very effective in controlling the side effects of chemotherapy but Dronabinol (Marinol) is a Schedule II THC drug. It can only be obtained by prescription through physicians registered with the National Cancer Institute and the DEA. Two synthetic cannabinoids seem promising; Nabilone, which has also been used in Europe and the United States to treat nausea and vomiting and beginning in 2006, Rimonabant, a CBI cannabinoid receptor antagonist has used to treat obesity in the United Kingdom but withdrawn from the market because of adverse psychiatric effects. In addition to using THC in the treatment of these conditions, the National Academy of Sciences concluded that THC/marijuana might also be useful in treating seizures, spasticity, and other nervous system disorders.

Recently, some states have voted to allow physicians to recommend marijuana for medical use, particularly for AIDS patients and terminally ill cancer patients. The effect of THC (e.g., Drabinol, Nabilone) in pain management has yielded inconsistent results. While there is insufficient research evidence for some of these therapeutic benefits, the controlled use of marijuana for patients with few other options constitutes a valid benefit-risk decision by physicians.

Medical Consequences of Cannabis Use

Although marijuana is not as dangerous as alcohol, for example (marijuana has no major effects on the liver or gastrointestinal tract), it is addicting and produces craving, in about 9 percent of users. Synthetic cannabinoids are more harmful than the cannabinoids found in nature. Regular users have difficulty abstaining and withdrawal symptoms including headaches, anxiety, depression and irritability have been reported.

Cardiovascular System

One of the most consistent and detectable effects of acute marijuana intoxication is a dose-dependent increase in heart rate (tachycardia). A normal resting heart rate is about 70 to 90 beats per minute. During intoxication, tachycardia of 20 to 50 beats per minute above normal is average and 140 beats per minute is not uncommon. The effects of marijuana on blood pressure are variable. For example, there is evidence that while intoxicated, blood pressure is increased while lying down, but decreased when standing. Tachycardia can increase the risk of stroke, heart disease and other cardiovascular problems and is a particular risk factor to individuals with existing cardiovascular or cerebrovascular diseases or pulmonary disorders. Daily but not monthly use of marijuana is associated with cardiovascular problems.

Schizophrenia

Case reports of patients using marijuana having psychotic symptoms (e.g., hallucinations, delusions, amnesia, paranoia) have been reported, but they are rare. Many studies linking marijuana use with psychotic disorders such as schizophrenia involve large doses or uncontrolled studies and often wide ranging definitions of “acute psychosis”. Also, many marijuana smokers may use other drugs that contribute to their psychotic-like behavior. One 15-year longitudinal study that controlled for premorbid characteristics, and which has been replicated, did show that adolescent or early use of marijuana is associated with a significant increase in psychotic disorders later in life. It is not clear if some subjects were predisposed to schizophrenia to begin with and also smoked marijuana. Cannabis use may be a risk factor for schizophrenia and predict poor outcome in existing schizophrenics. Ultimately, the

causal relationship between psychosis and marijuana remains controversial but there is increasing evidence that such a relationship exists.

Panic Attacks

Although less often reported, anxiety, depression, and paranoia may occur, usually following high doses of THC. The incidence of these is quite low, but may be more common among less experienced marijuana users. Regardless of experience, panic attacks can be quite serious. Should such a reaction occur, get the person to a hospital emergency room. The following treatment guidelines may be helpful.

First, determine if other intoxicating drugs or preexisting medical disorders are contributing to the symptoms. This can be accomplished through oral report of the user, witnesses, and/or a blood or urine drug screen.

Second, the patient should be assured that “it is only a drug” and the symptoms will stop in less than five to eight hours. Decreasing outside stimulation by placing the patient in a quiet room and “talking them down” is also helpful. Generally, the use of other drugs to treat a panic attack is not recommended unless the reaction is uncontrollable. Under such circumstances and with consultation, an anxiolytic such as alprazolam (Xanax), 6 mg daily, can be prescribed for a limited period.

Finally, patients should be warned that the drug will remain in the body for several days and that they may experience mild drug effects during that time and reassured that the effects are not permanent.

Brain Damage and Cognitive Functioning

Ultimately, the effects of marijuana on behavior are mediated by changes in the central nervous system. As a result, considerable attention has been given to identifying brain changes following marijuana use. Early studies demonstrated brain atrophy, reflected by enlarged ventricles within the brain or abnormal electroencephalogram (EEG) following marijuana use. For the most part, these studies demonstrated changes in these measures but not clearly so. For example, subsequent research found regular marijuana use in adolescence reduces the volume of brain areas involved in executive functions such as learning and impulse control, and that the degree of impairment in cognitive skills depends on age of initial drug use and duration of

use. These findings are consistent with animal studies demonstrating early exposure to THC (prenatal or different periods after birth) exhibit structural changes in the hippocampus, that part of the cortex responsible for learning and memory (see Chapter 2). However, motivation, learning and goal orientation are influenced by many social and environmental factors, one of which is drug use. Similarly, enhanced brain alpha wave activity (dominant when awake but not concentrating) and decreased beta wave activity (dominant when awake, focused and engaged in activities) were logical effects of marijuana use. However, these acute effects are not cannabis-specific, or surprising, since they occur with many sedative drugs. Moreover, it should be kept in mind that EEG changes occur constantly in the normal, drug-free brain. Non-drug studies have suggested that alpha activity is associated with a relaxed mental state whereas beta activity is associated with problem solving and other mental activities. Although some studies have demonstrated that THC can produce specific changes in the electrical activity of specific brain cells in animals, the relationship between such changes and behavior remains to be determined.

While the brain research continues for specific neurophysiological or anatomical changes as a result of marijuana use, other studies focus on the behavioral outcome of marijuana use. Longitudinal studies that account for other drug use, demographics and co-morbid psychiatric disorders suggest that marijuana use is associated with significantly lower verbal memory skills. Deficits in attention, memory and learning after acute marijuana use may last for days suggesting that regular use of this drug may result in a steady state of lower cognitive functioning. This is consistent with research reviews indicating that students who use marijuana have reduced educational achievements including lower high school graduation rates and a greater likelihood of developing dependence, use other drugs, attempt suicide, engage in criminal activity and feel lower levels of satisfaction in life. Clearly, other factors influence outcomes but there is no apparent benefit to marijuana use and short- or long-term impairment of cognitive skills will not result in improved performance. Currently underway is the Adolescent Brain Cognitive Development (ABCD) study. This is a landmark longitudinal study that will examine and track large samples of young participants, including twins. Testing and data collection from childhood (before first use of drugs) to early adulthood will collect data on genetics, cognitive abilities, neural imaging and factors to determine to what extent prenatal marijuana use or use during adolescent development affect brain development and behavioral outcomes.

Cancer

Cannabinoid medications (such as Dronabinol and Nabilone) are recognized in treating pain and the side effects of chemotherapy used to treat cancer. Even so, that benefit should not obscure the fact of an increasing scientific literature indicating that the combustion of marijuana, like tobacco leaf, produces tars and other products that increase the risk of lung cancer. For many years, advocates of marijuana use suggested that it was less harmful to smoke marijuana than it was to smoke cigarettes. That no longer seems to be true. Smoking marijuana is associated with aerodigestive (i.e., the oral cavity, sinonasal tract, larynx, pyriform sinus, pharynx and esophagus) cancers and cellular mutations related to tumors (much like tobacco). Although heavy users probably smoke fewer marijuana cigarettes than the average heavy tobacco user smokes, a typical joint contains two to three times the amount of tar found in some popular brands of cigarettes. Coupled with the fact that, like many cigarette smokers, marijuana smokers inhale deeply and hold the smoke to maximize the intake of the drug, the risk of pulmonary diseases as well as lung cancer is sufficiently strong to warrant concern among chronic marijuana users. To date, The American Cancer Society has not taken a position on the legalization of marijuana but it opposes smoking marijuana in public areas because the carcinogens in smoke present a health risk to the smoker and others. The interaction of smoking marijuana and cancer may be compounded by the effects of THC on immune system function.

Immune System

The immune system is made up of specialized cells (lymphocytes) that protect us from invading infectious or allergic diseases. By quickly responding to invading antigens, the body's immune system can combat many illnesses. There is some evidence that chronic marijuana use decreases the functioning of the immune system when measured strictly in terms of immunological response. However, it is not known whether such changes have any clinical significance or what the mechanisms of these effects are. For example, what are the effects from the action of THC, fungi, and molds or other contaminants on the plant or other factors? In other words, marijuana seems to impair the immune system in scientific studies, but the clinical significance is still under investigation.

Sex Hormones

Marijuana use reduces testosterone, the male sex hormone responsible for the development of secondary sexual characteristics and sperm cell production. Researchers have found that in humans, after four to six weeks of daily use, testosterone levels are depressed but still within normal limits. There is evidence that THC temporarily decreases levels of luteinizing hormone, a reproductive hormone in females. The clinical significance of this effect or the effect of chronic THC use in humans requires further study.

Toxicity

Although smoking marijuana results in tachycardia, hypertension, cognitive impairment (that may contribute to accidental deaths), in comparison to other psychoactive drugs, THC does not seem to be very lethal, although there have been several case-study reports of fatal overdoses in humans. In experimental studies, dogs given extremely high doses of THC survived. Statistical projections from animal data to humans suggest that there is about a 20,000-fold difference between therapeutic doses of THC and the lethal dose but such projections are only estimates. Synthetic cannabinoids (K2/Spice), when used in combination with synthetic opioids such as fentanyl can result in toxic overdose reactions. Generally, marijuana use does not result in toxic or fatal overdoses in the overwhelming majority of users.

Fetal Effects

It is difficult to measure marijuana effects on the fetus, because few women use only marijuana during pregnancy. More often, other variables such as alcohol smoking cigarettes, and poor prenatal care produce an unclear picture. Although THC does cross the placental barrier, most studies still reveal no clear relationship between maternal marijuana use and physical birth defects in humans. Studies reporting some defects such as craniofacial features similar to FAS, reduced birth weight and length have not been consistent. At birth, marijuana-exposed infants may have poorer habituation to visual stimuli, fine tremors, and increased startle responses to spontaneous and mild stimuli. Although many adverse cognitive and behavioral effects can

be seen during the first month, by 1–2 years of age, differences in mental, visual, and motor performance are not observed. Subtle, long-term effects are more difficult to detect.

There is some evidence that marijuana use causes chromosomal damage in some cells. Chromosomes are components within the nucleus of cells that carry the genetic information unique to each individual and necessary for cell replication and reproduction. There is also evidence that marijuana does *not* affect chromosomes. Even though the mechanism of any marijuana effects on the fetus have not yet been identified, the safe public health message is that marijuana use during pregnancy should be avoided. Cannabinoids used by the mother do pass into the fetus and can be detected in newborns. Moreover, relatively high concentrations of THC are also secreted into the milk of nursing mothers. Hence, the use of marijuana during nursing should also be avoided.

Finally, since marijuana impairs memory and other cognitive skills in emergency situations, marijuana use should be avoided during childcare in general. Even though the research on marijuana use during pregnancy is not conclusive, recommendations that pregnant women should abstain from marijuana use during pregnancy is probably justified.

Tolerance and Dependence

Under laboratory conditions, the administration of THC several times a day for several days in humans results in tolerance to the effects of marijuana on mood, body temperature, intraocular pressure and impairment of psychomotor skills. Outside of the lab, tolerance also develops, although many chronic users claim that they need less of the drug the more they use it. This suggests that at least some aspects of “reverse” tolerance may be due to learning. In other words, the experienced smoker has learned what effects to focus on to enhance the high. Alternatively, this effect may be due to the slow release into the blood of active metabolites stored in fatty tissue. Hence, the baseline blood levels of THC or its metabolites are greater than zero in the chronic user and thus it appears that less drug is needed to get high.

In laboratory animal studies, high doses of marijuana every four hours (for 10 to 20 days) cause mild withdrawal symptoms when the drug is abruptly discontinued. By operational definition, this means that THC causes physical dependence. However, physical withdrawal signs may be observed in patients

Table 13.2 Signs and Symptoms of Marijuana Withdrawal*

<ul style="list-style-type: none">• Decrease in mood• Decrease in appetite• Irritability and restlessness• Generalized anxiety• Depression• Hostility• Difficulty sleeping• Excessive sweating• Diarrhea• "Low-grade" flu symptoms• "Inner unrest"
--

*Most symptoms begin with 1–3 days of abstinence and last for 10–14 days and can vary considerably between individuals.

undergoing treatment for marijuana dependence in hospitals, especially if the patient is observed for several days after marijuana cessation, since withdrawal signs tend to be delayed in patients due to high fat solubility of THC and metabolites. While there are many anecdotal stories about withdrawal, most sources agree that the withdrawal syndrome associated with marijuana is similar to that of tobacco but less severe than withdrawal from opioids or alcohol. There are no documented cases of deaths from marijuana withdrawal (see Table 13.2 for symptoms of withdrawal).

Forensic Considerations

Marijuana and Criminal Activity: History, Lessons and Current State of Knowledge

At about the same time as the alcohol prohibition movement started gaining momentum in the United States, newspaper articles linking marijuana use to violent crime attracted public interest and concern. The link between marijuana use and violence stemmed from a few isolated incidents and there was no concrete evidence that marijuana caused violence. Movies such as *Reefer Madness* were widely distributed to dissuade young people from using this drug and were not based on factual evidence. Nevertheless, by 1936 most of the United States had laws regulating the use, sale and possession of cannabis. These regulations coupled with a very high tax on growers,

distributors, and buyers made legal use of cannabis almost impossible. In 1969 the U.S. Supreme Court declared that a marijuana “tax law” was unconstitutional because it violated the Fifth Amendment. Since this constitutional amendment protects people from self-incrimination, declaring marijuana use on your tax return would be in violation of a constitutional right and of the Fifth Amendment.

Despite major legislation aimed at preventing the use of marijuana and considerable speculation about its harmful effects, there had been little scientific research on the drug up through the 1930s and 1940s. To determine what course of legal action should be taken to protect the public from the consequences of marijuana use, New York City Mayor Fiorello LaGuardia asked the New York Academy of Medicine to look into the matter. The academy issued a report in 1944 in which they concluded that the acute use of marijuana impaired intellectual functioning but did not alter the basic personality of users, nor did chronic use produce mental or physical deterioration. Although this report met with violent criticism from the American Medical Association, the LaGuardia Report agrees with previous studies as well as subsequent ones. Although engaging in purchase and use of any illegal item will expose people to a criminal element, there is no evidence that smoking marijuana causes violent or aggressive behavior. If marijuana use increased crime, one might expect that the prevalence or density of medical marijuana dispensaries to be associated with an increased crime rate in those areas. Preliminary research shows that not to be the case.

As with other drugs, such as alcohol, marijuana intoxication impairs many cognitive functions, including judgment, which can lead to poor decisions regarding present behavior and future outcomes. However, there is little scientific evidence that marijuana use is associated with an increase in violent or aggressive behavior.

Motor Vehicle Operation

Earlier studies on the effect of THC on motor vehicle crashes produced highly variable results. Epidemiological studies often based the relationship between motor vehicle accidents and THC on “positive” findings of THC in urine and in laboratory studies as well as field studies, the concentration of THC in blood did not always correlate with impairment for a different reason. We now know that the effects of THC are greatest shortly after use

and diminish significantly after about 3 hours. With few exceptions, there are few significant biobehavioral effects after about 4 hours. The application of pharmacokinetics to determine intoxication is also discussed in Chapter 18 (Forensic Issues).

Forensic science is the application of principles of or scientific evidence applied to matters of law. Since the last edition of DBB, the legal landscape regarding marijuana use has changed dramatically. Laws and penalties vary between states and most states still distinguish between possession for personal use and possession with intent to sell, which carries more severe penalties. It is also still against the law to operate a motor vehicle under the influence of THC with penalties similar to drunk driving. Unlike alcohol, there is no general agreement as to a blood cannabinoid threshold above which it can be concluded a driver is impaired. Most states that have legalized marijuana use have seen an increase in marijuana/THC related motor vehicle accidents. Statistics from Colorado, one of the first states to legalize marijuana in the United States, indicated that since recreational marijuana was legalized, motor vehicle fatalities increased 138% in comparison to a 29 percent increase for all Colorado traffic deaths and fatalities involving drivers who tested positive for THC. Even though laboratory studies have reported cognitive, physiological and psychomotor effects of cannabinoids and driving simulator studies also show impairment, research on the effects of cannabinoids in motor vehicle crashes and increased risk are inconsistent. Nevertheless, driving or similar behaviors that require alertness and psychomotor control preclude the use of marijuana prior to engaging in similar tasks.

Since the penalties associated with marijuana use vary considerably, please consult the particular laws of your state for more information about current laws in your jurisdiction.

Laboratory Detection of THC

THC has a rapid distribution half-life and blood concentrations drop rapidly to low levels within about five hours of use. From that point, THC slowly continues to be metabolized and eliminated. After distribution, THC has a metabolic half-life of 20–57 hours in infrequent users, and 3–13 days in frequent users. Inactive THC metabolites can be detected in urine for as many as 45 to 60 days after the last use, depending upon the method of analysis and how often the subject smokes marijuana. Because THC and its metabolites

are highly fat soluble, these compounds are stored in, and slowly released from, fat tissue. This has two implications: the first is that by analyzing a sample of blood or urine, it is easy to determine whether or not someone has used marijuana in the last month or two. Second, the test alone does not provide bona fide evidence that the person was intoxicated at the time of testing (see below). Behavioral evidence of intoxication or other indications of recent use are needed for such a conclusion. Marijuana can be detected in most body fluids, including serum, blood, saliva or urine, using a variety of analytical methods, including thin layer chromatography (TLC), high pressure liquid chromatography (HPLC), gas chromatography (GC), gas chromatography/mass spectrometry (GC/MS), enzyme immunoassay (EIA) and radioimmunoassay (RIA).

These laboratory tests are used to detect THC compounds. The more sensitive tests are also the most expensive to run. The EMIT test of urine is sensitive down to 20 nanograms per milliliter (ng/ml). SAMHSA (Substance Abuse and Mental Health Service Administration) has set the cut-off limit to report a positive drug finding at 50 ng/mL. TLC and RIA tests are capable of detecting THC or its metabolites in the 1–5 ng/ml range and GC/MS can detect as little as 0.5–1 ng/ml. Since 1 nanogram is equal to 1/1,000,000,000th of a gram and 1 ml (milliliter) is equal to about 1/30 of a fluid ounce, you can see that these tests are extremely sensitive. Depending on the actual dose, smoking two joints, one every two hours, will raise plasma D-9-THC in the blood to roughly 40–50 ng/ml within ten minutes. Yet six hours after the second joint, D-9-THC levels are still around 5 ng/ml. THC metabolites can be detected in urine weeks or months after the last dose.

While these tests are accurate and obviously quite sensitive, they may not be quantitative. In many cases, laboratories detect THC through the presence of metabolites only. Since not all metabolites are psychoactive, a “positive for THC” test in body fluids does not necessarily provide scientific information about (1) how much was administered, (2) when the drug was taken, or (3) the effect of the drug on behavior or physiology. Most forensic and clinical urine tests for THC measure the major metabolite 11-nor-9-carboxy-D-9-THC (9-carboxy-THC), which itself is not psychoactive. In fact, there is some concern that with extremely sensitive test procedures, people who passively inhale marijuana smoke or who are exposed to other forms of involuntary consumption of THC would test positive for the drug. Studies on passive inhalation or absorption through the skin (from handling marijuana) have not been conclusive.

Selected Bibliography

- Agurel, S. L. and Hollister, L. E. (1986). Pharmacokinetics and metabolism of delta-9-tetrahydrocannabinol: Relations to effects in man. *Alcohol, Drugs and Driving*, 2: 61–77.
- American College of Cardiology (2023). Frequent Marijuana Use Linked to Heart Disease. February 24, 2023.
- Baselt, R. C. (2008). *Disposition of toxic drugs and chemicals in man*, 8th Edition, Foster City, CA: Biomedical Publications.
- Booth, M. (2004). *Cannabis: A history*. London: Bantam Publishing.
- Brick, J. (1990). *Marijuana*. New Brunswick, NJ: Rutgers University Center of Alcohol Studies.
- Budney, A., Moore, B. and Vandrey, R. (2008). Health consequences of marijuana use. In: J. Brick (Ed.), *Handbook of the medical consequences of alcohol and drug abuse*. Haworth Press, Taylor Francis Group, pp. 251–301.
- Canavan, D. I. (1987). Screening: Urine drug tests. *Maryland Medical Journal*, 36: 229–233.
- Centers for Disease Control and Prevention, National Center for Injury Prevention and Control. Last reviewed: January 5, 2023.
- Chait, L. and Pierri, J. (1992). Effect of smoked marijuana on human performance: A critical review. In: L. Murphy and A. Bartke (Eds.), *Marijuana/cannabinoids: Neurobiology and neurophysiology*. Boca Raton, FL: CRC Press, pp. 387–425.
- Chiang, C. N. and Rapaka, R. S. (1987). Pharmacokinetics and disposition of cannabinoids. In: R. S. Rapaka and A. Makriyannis (Eds), *Structure-activity relationships of the cannabinoids*. Rockville, MD: National Institute on Drug Abuse, U.S. Department of Health and Human Services, Research Monograph 79.
- Department of Health and Human Services (1987). *Drug abuse and drug abuse research: Marijuana and cannabinoids. The second triennial report to congress from the secretary, Department of Health and Human Services*, ADAMHA, NIAAA. Rockville, MD: Author, pp. 77–91.
- Dickson, S. and Poulsen, H. (2014). Cannabis. In: *Wiley encyclopedia of forensic science*. ISBN 9780470061589, DOI: 10.1002/9780470061589
- DiForti, M., Morgan, C. and Dazzan, P. (2009). High-potency cannabis and the risk of psychosis. *RIT Journal of Psychiatry*, 195: 488–491.
- Ellis, G. M., Mann, M. A., Judson, B. A., Schramm, N. T. and Taschian, A. (1985). Excretion patterns of cannabinoid metabolites after last use in a group of chronic users. *Clinical Pharmacology of Therapeutics*, 38: 572–578.
- Erickson, C. (1992). A comment on marijuana and a recent paper. *Science Matters*, 2(6): 21, 24.
- Fehr O'Brien, K. and Kalant, H. (1983). Cannabis and health hazards. *Proceeding of an Addiction Research Foundation/World Health Organization scientific meeting on adverse health and behavioral consequences of cannabis use*. Toronto: Addiction Research Foundation.

- Garry, A., Rigour, V., Amirouche, A., Fauroux, V., Aubry, S. and Serreau, R. (2009). Cannabis and breastfeeding. *Journal of Toxicology*, 2009.
- Godin, S. L. and Shehata, S. (2022). Adolescent cannabis use and later development of schizophrenia: An updated systematic review of longitudinal studies. *Journal of Clinical Psychology*, 78(7): 1331–1340.
- Grinspoon, P. (2021). Cannabidiol (CBD): What we know and what we don't. www.health.harvard.edu/blog/cannabidiol-cbd-what-we-know-and-what-we-don-t-201808244476
- Hasan, A., von Keller, R., Friemel, C., Hall, W., Schneider, M., Koethe, D., Leweke, F. M., Strube, W. and Hoch, E. (2020). Cannabis use and psychosis: A review of reviews. *European Archives of Psychiatry and Clinical Neuroscience*, 270(4): 403–412.
- Heustis, M. (2002). Cannabis (marijuana) effects of human behavior and performance. *Forensic Science Review*, 14: 14.
- Heustis, M. (2015). Cannabis-impaired driving: A public health and safety concern. *Clinical Chemistry*, 61(10): 1223–1225.
- Howlett, A., Egans, D. and Houston, D. (1992). The cannabinoid receptor. In: L. Murphy and A. Bartke (Eds), *Marijuana/cannabinoids: Neurobiology and neurophysiology*. Boca Raton, FL: CRC Press, pp. 35–72.
- Johnston, L. D., O'Malley, P. M. and Bachman, J. G. (1988). *Illicit drug use, smoking, and drinking by America's high school students, college students and young adults: 1975–1987*. National Institute on Drug Abuse, U.S. Department of Health and Human Services Publication No. (ADM) 89–1602, Washington, DC: U.S. Government Printing Office.
- Johnston, L., O'Malley, P. and Bachman, J. (1996). *Monitoring the future study 1975–1996*. Rockville, MD: National Institute on Drug Abuse, U.S. Department of Health and Human Services.
- Keppel, N. and Freisthler, B. (2012). Exploring the ecological association between crime and medical marijuana dispensaries. *Journal of Studies on Alcohol and Drugs*, 73: 523–530.
- Levine, B. (2010). *Principles of forensic toxicology*. AACC Press.
- Logan, B., Mohr, A., Friscia, M., Krotulski, A., Papsun, D., Kacinko, S., Roper-Miller, J. and Huestis, M. (2022). Reports of adverse events associated with use of novel psychoactive substances, 2017–2020: A review. *Journal of Analytical Toxicology*, 46: e116–e185.
- Mackie, K. (2006). Cannabinoid receptors as therapeutic targets. *Annual Reviews of Pharmacology and Toxicology*, 46: 101–122.
- Manthey, J. (2019). Cannabis use in Europe: Current trends and public health concerns. *International Journal of Drug Policy*, 68: 93–96.
- Missouri Medicine (2021). The legalization of marijuana in Colorado: The impact. *Missouri Medicine*, 118(6): 534–535.
- NIDA (2018). Synthetic Cannabinoids (K2/Spice) DrugFacts. Retrieved from <https://nida.nih.gov/publications/drugfacts/synthetic-cannabinoids-k2spice> on May 8, 2023.

- Niedbala, R. S., Kardos, K. W., Fritch, D. F., Kunsman, K. P., Blum, K. A., Newland, G. A., Waga, J., Kurtz, L., Brongsgeest, M. and Cone, E. J.. (2005). Passive cannabis smoke exposure and oral fluid testing. II. Two studies of extreme cannabis smoke exposure in a motor vehicle. *Journal of Analytical Toxicology*, 29(7): 607–615.
- New York Times Magazine* (February 19, 1995). Marijuana in the 1990s. Section 6.
- Oberbarnscheidt, T. and Miller, N. (2020). The impact of cannabidiol on psychiatric and medical conditions. *Journal of Clinical Medicine Research*, 12(7): 393–403.
- Phillips, L. (1985). *Drug law enforcement training manual*. South Carolina Criminal Justice Academy.
- Ray, O. S. and Ksir, C. (1987). *Drugs, society and human behavior*, 4th Edition, St. Louis: Times Mirror/Mosby College Publishing, pp. 300–321.
- SAMHSA News, September/October 2010, Vol. 18, No. 5.
- SAMHSA. Center for Behavioral Health Statistics and Quality. National Survey on Drug Use and Health 2021.
- Schuckit, M. A. (1989). Cannabinols. In: M. A. Schuckit (Ed.), *Drug and alcohol abuse: A clinical guide to diagnosis and treatment*. New York: Plenum Medical Book Co., pp. 143–157.
- Smiley, A. (1986). Marijuana: On-road and driving simulator studies, *Alcohol, Drugs and Driving*, 2(3–4): 121–134.
- Spindle, T., Cone, E. J., Schlien, N. J., Mitchell, J. M., Bigelow, G. E., Flegel, R., Hayes, E. and Vandrey, R. (2019). Acute pharmacokinetic profile of smoked and vaporized cannabis in human blood and oral fluid. *Journal of Analytical Toxicology*, 43(4): 233–258.
- Spindle, T., Sholler, D., Cone, E., Murphy, T., ElSohly, M., Winecker, R., Flegel, R., Bonn-Miller, M. and Vandrey, R. (2022). Cannabinoid content and label accuracy of hemp-derived topical products available online and at national retail stores. *JAMA Network Open*, 5(7): e2223019. DOI:10.1001/jamanetworkopen.2022.23019
- Wu, T. C., Tashkin, O. P., Djahed, B. and Rose, J. E. (1988). Pulmonary hazards of smoking marijuana as compared with tobacco. *New England Journal of Medicine*, 318: 347–351.
- Yesavage, J., Leirer, V., Denari, M. and Hollister, L. (1985). Carry-over effects of marijuana intoxication on aircraft pilot performance: A preliminary report. *American Journal of Psychiatry*, 142: 1325–1329.

Hallucinogens: Altering Reality or Helping? 14

In previous chapters, we discussed pharmacotherapies that help people with mental illnesses, including antipsychotics to treat psychosis. In this chapter, we will discuss drugs that have pharmacological properties and effects that mimic some of the symptoms of major psychoses including hallucinations and altered reality. The drugs in this class tend to be old, some are still used in religious ceremonies in Native American and First Nation peoples, and some are newer recreational drugs that have what can only be described as weird rationales for use. Some of these (such as mushrooms and LSD) are a lot safer than many other drugs (e.g., inhalants), but many in the general population frown upon their recreational use. However, there has been a resurgence in interest in the use of psychedelics to treat psychiatric disorders.

Hallucinations, illusions and disorders of thinking (e.g., paranoia) can be produced with high, toxic doses of many drugs. Similar subjective effects may also occur during withdrawal from long term use of drugs such as alcohol as part of a constellation of signs and symptoms known as delirium tremens, or DTs. However, certain drugs (“hallucinogens”, “psychedelics”) can produce these effects as primary pharmacological actions at low doses.

What Are Hallucinogens?

Most major hallucinogenic or psychedelic compounds fall into two main molecular structures: *indolamines* or *phenethylamines*. Indolamines include

drugs like LSD. Previously, these compounds were called “serotonergic hallucinogens” because of their chemical structure and primary neuropharmacological action. The other structural group of hallucinogens is *phenethylamines* that include drugs like mescaline and some mixed stimulant like MDMA. Although there are other differences, both groups of hallucinogens involve an affinity for serotonin receptors in the brain and both produce hallucinations. When a sensory perception such as an auditory, tactile or visual hallucination occurs without an external cause, it is the result of a neurological condition such as a psychotic disorder, withdrawal from a drug (e.g., delirium tremens during alcohol withdrawal) or in response to a drug such as LSD, or phencyclidine. Hallucinations are different from “delusions”, which are false beliefs that are resistant to reality testing. Seeing a pink elephant during alcohol withdrawal is a hallucination; believing the pink elephants are your parents is a delusion. Finally, an “illusion” (also known as a misperception) is a distortion of a sensation (feeling, seeing, hearing, etc.) that exists, but perceived as something different. Drugs or physiological phenomena such as fever, infection, heat stroke, or other physical changes that affect the senses can cause illusions. For example, malaria or temperature inversion in the desert or a roadway may result in an optical illusion of water (e.g., a desert mirage). Such altered perceptions are unrelated to drug use.

History of Hallucinogen Use

For many centuries, humans have sought miraculous insights and cures from natural sources. A common theme in many of the world’s religions is the idea that animals, plants, rocks, and streams have magic properties that may emanate from a spirit within. Anthropologists refer to this as animism. To a degree, there is some truth to this belief. For example, long ago, plants that had the ability to alter a person’s perception of the world and of him/herself must have appeared magical, and they still hold a special place in some religious ceremonies, and of course in the world of recreational drug use. It is human nature, and the basis of many a novel and movie, to have an intrinsic desire to feel special, spiritual, powerful and at least happy for most of the time. Even in pharmacy, natural medicinals have been a special area of study. In the old days the study of useful plant ingredients was called “pharmacognosy”, but today it is the study of “herbal and nutritional remedies” (there is even a PDR of Herbal Medicine!). It is not too much of a stretch to say that the health discipline of pharmacy began many centuries ago when people

became familiar with mood-altering plants. “Medicine men” with special knowledge of these plants peddled them and their active ingredients (opium, coca leaves, “magic mushrooms” and others) to people who were seeking less pain, suffering, fatigue, and boredom. Such practices and interests in plant products continue today.

The most well-known hallucinogen is probably LSD. Albert Hoffman first synthesized LSD (lysergic acid diethylamide) in 1938. Early investigation of its uses included therapy for mental illness and as a chemical warfare weapon. It was popularized by American psychologists Timothy Leary and Richard Alpert. Together they began the Harvard Psilocybin Project to study the effects of this entheogenic (plant derived) hallucinogen on human consciousness and by the “hippies” of the 1960s, as a way to explore their own consciousness and feelings. Both Leary and Alpert were eventually fired from Harvard for their unorthodox and controversial methods. In the Haight-Ashbury district of San Francisco, “dropping acid” was emblematic of drug use in that era, as users followed Dr. Leary’s slogan “Tune in, turn on, and drop out”. Scientific research on LSD virtually stopped in the early 1970s, but some people continued to explore the drug personally (although rates of LSD use have always been low compared to other drugs). More recently there has been a renewal of interest in LSD and other psychedelics for epidemiologic purposes, as well as in the treatment of depression, anxiety, headache, other pain and drug addiction.

There are two broad categories of hallucinogens, based on their neuropharmacological action: psychedelic hallucinogens that act as serotonin receptor (5-HT_{2A}) agonists (e.g., LSD, psilocybin, dimethyltryptamine [DMT] and mescaline) and entactogens (also termed empathogens) that act as serotonin releasing agents (e.g., MDMA).

Common Hallucinogens

Table 14.1 shows a list of common hallucinogens.

Dimethyltryptamine (DMT) is a naturally-occurring psychedelic compound that is ubiquitous in plants. Because digestive juices destroy the active ingredients, it is taken in snuff, smoked, or by injection. It is the main ingredient in Cohoba snuff, which is used by some South American Indians. Its actions are characterized as being “brief”, lasting only about an hour, leading to the drug’s nickname of “businessman’s trip”.

Table 14.1 Common Hallucinogens Available Around the World

-
- LSD (d-lysergic acid diethylamide)
 - DMT (dimethyltryptamine)
 - Psilocybin (mushrooms)
 - PCP (phencyclidine)
 - Mescaline (from the Peyote cactus)
 - DOM (dimethoxymethyl-amphetamine), STP
 - MDMA (ecstasy)
 - “Bath salts” (synthetic stimulants, such as mephedrone, MDPV and methylone)*
 - *Salvia divinorum* (salvia plant)
 - Synthetic cannabis (K2, Spice)*
 - Ketamine (dissociative anesthetic)*
-

*Not strictly hallucinogens; may or may not produce hallucinations.

Psilocybin is a psychedelic compound found in more than 200 species of “magic mushrooms”. The mushroom that has the greatest psychoactive effect is *Psilocybe Mexicana*. The primary active ingredient in this mushroom is psilocybin, which Albert Hoffman isolated in 1958 and later synthesized. The dried mushrooms contain 0.2–0.5 percent of psilocybin, and the hallucinogenic effects are similar to those of LSD and mescaline.

Phencyclidine (PCP) was originally developed as an anesthetic but its use was discontinued in 1965 because of serious adverse effects. Like ketamine, it produces an extreme “out of body” experience that can result in severe agitation, irrational fear and death (suicide or accidental) injury due to the effects of placing the user in situations not well suited for the dissociative effects of this drug.

Mescaline is the active ingredient in peyote and the San Pedro cacti. Synthetic mescaline, isolated in 1890, is a thin crystal sold in capsules. The cacti are still eaten in ritual ceremonies by the northern Mexican tribes, and by the Southwest Plains Native American tribes. In addition, the Native American Church of North America also uses the peyote cactus as a sacrament. Mescaline induces a psychedelic state similar to those produced by LSD and psilocybin, but different subjective effects that may include altered thinking processes, an altered sense of time and self-awareness, and closed and open-eye visual phenomena. Colors are distinctive, appearing brilliant and intense.

Dimethoxymethyl-amphetamine (DOM), also known as STP (for “serenity”, “tranquility”, and “peace”) is similar to MDA, a synthetic

amphetamine-like drug that was widely used illegally before the 1990s, the use of which has now been taken over by MDMA. DOM causes a 12-hour intoxication characterized by intense stimulation and mild psychedelic reactions. DOM use has declined over the years because of reported higher incidences of acute and chronic toxic reactions as compared to other hallucinogens.

MDMA (methylenedioxymethamphetamine) is a synthetic, psychoactive drug that is chemically a mixture of methamphetamine and mescaline. Its interesting history is characterized by its use being supported by many psychiatrists who insisted it is not a true hallucinogen; rather, it has a special ability to promote empathy, which aids the psychoanalytic process. Many people taking MDMA (Ecstasy, Molly, XTC) indeed report that they experience a heightened sense of “closeness” with other people. Clinical trials are now testing MDMA’s therapeutic potential for post-traumatic stress disorder (PTSD) and anxiety associated with terminal cancer. MDMA is classified as a “club drug”, since it is commonly associated with dance parties (“raves”) and electronic dance music.

Ketamine is an anesthetic used in veterinary and human medicine. High doses (9–13 mg/kg) has anesthetic effects whereas low doses (.01–0.5 mg/kg) may have psychotherapeutic value when used in treatment of depression, although this effect is short lived (1 to 7 days).

There are also multiple “designer drugs” that pharmacologists and chemists know little about, and which may or may not produce hallucinations or neurological effects. These include “bath salts” (not bath salts at all; rather, street drugs often containing synthetic stimulants such as mephedrone, MDPV (a stimulant) and methylone (a glucocorticoid)) and synthetic cannabis (known as K2 and Spice). Too often “bathtub chemists” can create new recreational drugs faster than legislation can be established to outlaw them. Caveat emptor (let the buyer beware...).

Absorption, Distribution, and Metabolism of Hallucinogens

Some hallucinogens, such as synthetic cannabinoids (e.g., K2/Spice are smoked and enter through the respiratory system). However, most hallucinogens are consumed by mouth and absorbed into the circulation through the gastrointestinal system. For example, absorption of LSD from the gastrointestinal tract is rapid; but the brain takes up LSD more slowly than

any other organ, which makes its onset rather slow (45–60 minutes). Half of the LSD in the blood is such that the concentration of drug decreases by 50 percent every 3–4 hours. The metabolism of LSD has not been thoroughly investigated in humans; however, through animal studies LSD is known to undergo biotransformation in the liver to inactive metabolites.

LSD is one of the most potent hallucinogenic agents known, especially with such a low acute toxicity. The therapeutic index (difference between useful dose and lethal dose) is around 1000. Problem drug users usually take LSD as the tartrate salt in oral doses of 25–250 mg. It is often thought that LSD has no known lethal dose in humans, but in fact a case directly attributed to LSD was reported in 1985 in which a 25-year-old male died 16 hours after hospital admission.

Doses of DMT (Dimethyltryptamine) are in the range of 50–150 mg, commonly applied to tobacco, marijuana, or other plant leaves and smoked. DMT causes intense visual hallucinations, intoxication, and often a loss of awareness of surroundings for about 30 minutes or less. It is rapidly and extensively metabolized in the liver, yielding 3-indoleacetic acid. The half-life of the drug in the blood is from 30 minutes to 1.5 hours.

A typical single, oral hallucinogenic dose of psilocybin is 10 mg, which would usually be found in about 1 g of fresh mushroom, although mushroom concentrations vary widely within and among species. Psychic effects of these doses generally last 5–6 hours (half-life of the drug in the blood is about 2–4 hours). In humans, psilocybin undergoes rapid conversion to psilocin, which has less potency than psilocybin, which can be found in the urine after metabolism.

An oral hallucinogenic dose of mescaline is about 200–500 mg as hydrochloride or sulfate salt. Mescaline is readily absorbed when taken orally, but does not pass through the blood-brain barrier readily (thus high doses of the drug are needed for effect). The effects of such doses last up to about 12 hours (the half-life of the substance in the blood is about 6 hours). Most of the drug is excreted unchanged in metabolites in the urine, and all of these metabolites are believed to be pharmacologically inactive.

The actions and effects of DOM (Dimethoxy-4-methylamphetamine) are very similar to those of mescaline and LSD, with 3–5 mg of the drug leading to a 6–8-hour hallucinogenic period. Thus, DOM is about 100 times as potent as mescaline, but only 1/30 as potent as LSD. The allegedly long experience produced by DOM is probably due to the high doses sold on the street.

MDMA (Methylenedioxymethamphetamine/ecstasy) is usually taken in oral doses of 100–150 mg as hydrochloride salt. The effects of the drug are felt in 20–60 minutes after oral ingestion (sooner after injection), and they last from 4–6 hours. MDMA is metabolized in the liver to MDA, and a single dose is eliminated in the 24-hour urine as MDMA (26 percent), MDA (1 percent) and three metabolites. MDA (Methylenedioxyamphetamine) is also psychoactive.

Pharmacology of Hallucinogens

The pharmacology (mechanism of drug action) of psychedelics has not been completely established. In general, they share an affinity (attraction) for serotonin 5-HT₂ receptors, but they differ in their affinity for other types of serotonin receptors. In fact, their affinity for 5-HT₂ receptors correlates well with their hallucinogenic qualities in humans. Antagonists of those receptor subtypes can effectively block the behavioral and electrophysiological effects of hallucinogens in animal models.

We might expect that the mechanisms of action of other psychedelic drugs would be similar to that of LSD; however, all of them have slightly different behavioral qualities than LSD and many act on specific subsets of receptors within one neurochemical system such as the indolamine, serotonin (5-HT). Among these receptor subsets are 5-HT 1A, 5-HT 2A, 5-HT 2B, 5-HT 2C, 5-HT 6 and 5-HT 7). With renewed interest in, and evidence that hallucinogens may be effective in treating mental illnesses we may see more research and application of these drugs in the future.

Biobehavioral Effects of Hallucinogens

The biological and behavioral effects of the hallucinogens as a group include, of course, frank hallucinations at various doses depending upon the specific drug in question, and the potency of the drug. LSD is by far the most potent (meaning the fewest number of molecules is required to produce an effect), with doses in the microgram range. All the other hallucinogen drugs require milligram doses (micrograms times 1000) to exert their effects. LSD and MDMA (ecstasy) are unique in their ability to raise body temperature (especially MDMA, sometimes to lethal levels). Most of the psychedelics also cause

a rise in heart rate and blood pressure, dizziness, dilated pupils and some sweating, much like amphetamines. With LSD, users see many light trails, much like after-images in old-time television sets. This aftereffect is known as the “trailing phenomenon”.

Mentally, LSD affects the brain stem, causing sensory distortions (seeing sounds, feeling odors or hearing colors – known as synesthesias). There is also dreaminess, depersonalization, altered mood, impaired concentration and motivation, difficulty in expressing oneself verbally (with non-sequiturs and single-word answers predominating). LSD is also similar to other intoxicants in its ability to reduce judgment and to impair reasoning, and to slow reaction time and produce visual distortions – thus making it dangerous to drive a car. While LSD’s toxicity is low, users can often lose their lives by jumping off a building, trying to race a train to a railroad crossing, or taking other risky chances by thinking that they can do superhuman tasks.

LSD is the prototype hallucinogenic drug, the one to which all others are compared. MDMA (ecstasy) is the most popular psychedelic drug among users, with similar effects as LSD, lower potency and more direct toxic effects on the brain (see below). DOM is not very popular these days; psilocybin (mushrooms) and mescaline are used by some psychedelic seekers, but mostly in native religious ceremonies.

Medical Use of Hallucinogens

The treatment of clinical depression often involves medications that increase the functional activity of brain serotonin (see Chapter 6). It should not be surprising that hallucinogenic drugs that affect brain serotonin have some potential psychotherapeutic use. This is a complex field in terms of the neurophysiology but the results from a number of studies have led to the hypothesis that LSD and psilocybin increase sensory processing coupled with reduced associative networks in the brain which may create a different perception of self and environment allowing patients to be less rigid or ruminative in their thinking. Low doses of hallucinogens may improve mood, increase sociability and create a normalizing effect on the brain. Low doses of ketamine, a dissociative anesthetic often described as a hallucinogen has been demonstrated repeatedly to have antidepressant properties producing faster results (hours compared with many days) as compared with traditional antidepressants.

MDMA when combined with behavioral therapy appears to be effective in treating posttraumatic stress disorder (PTSD). The potential benefit of MDMA appears only when combined with psychotherapy and not when used alone. One effect of MDMA is that it acts as an empathogen that creates an interpersonal bond between people. This might explain why MDMA appears effective when combined with guided behavioral therapy. Other hallucinogens including LSD show some promise in treating depression and anxiety. More research is needed to understand the mechanisms and efficacy of hallucinogens in treatment.

Medical Consequences of Hallucinogen Use

One of the problems with identifying the toxicology of street drugs such as LSD is the purity of the sample. There is no easy way to provide a reliable metric on the incidence of adverse reactions to LSD. However, putting anecdotal stories of peoples' usage of LSD together with some of the literature can provide us with some ideas about toxicity. One of the facts we do know is that the toxic effects of LSD do not match the potency; i.e., just because LSD only requires micrograms to produce hallucinations does not mean it has high lethality, and perhaps not even high toxicity to other organs.

Psychological Effects

The most well-known toxic effects of LSD to users are the so-called "bad trips" and flashbacks. These are not the same. "Bad trips" are acute anxiety reactions usually seen in first-time users who do not expect the effects they finally feel and observe. LSD typically affects emotions and distorts reality, and these reactions often lead to extremes of euphoria and panic. The phenomena of depersonalization and lack of a stable environment can trigger acute anxiety, paranoia, fear of loss of control, and delusions of persecution or feelings of grandeur leading to dangerous behaviors. An example would be a person who jumped from a bridge into a "sea of eternity".

Flashbacks are recurrences of symptoms weeks or months after the use of LSD, with no current use of the drug, and which are quite variable and unpredictable. They are most frequent just before going to sleep, while driving, or during psychological stress. They have been explained in various ways; psychologically they may be attempts to resolve and master traumatic experiences.

Table 14.2 Signs and Symptoms of Hallucinogen Use

<ul style="list-style-type: none">• Marked anxiety or depression• Fear of losing one's mind• Paranoid ideation• Impaired judgment• Impaired social or occupational functioning• Depersonalization• Illusions• Hallucinations (generally visual)• Synesthesias (mixed senses, such as seeing a sound)• Pupillary dilation• Incoordination• Tachycardia (rapid heartbeat)• Palpitations (skipped heart beats)• Sweating• Blurred vision• Tremors• Incoordination
--

Neurobiologically, they may simply be past memories triggered by environmental or psychological stimuli. In any case, if the person no longer uses LSD, the frequency of the flashbacks will become reduced over time.

An apparent myth about LSD toxicity is that LSD increases creativity in art, writing or philosophical thought. To some extent, other drugs such as alcohol allegedly have similar effects, but there is no convincing evidence that any drug can increase creativity. Another myth about LSD is that it causes damage to chromosomes, leading to birth defects and cancer in humans. While such stories may seem potentially useful for reducing LSD use in the population, there is no evidence behind such “stories”.

LSD exhibits most of the signs of hallucinogen use as a group, which are shown in Table 14.2. These effects may vary depending upon dose, environment or expectation of the user.

Hallucinogen use/problem use has declined over the past decades. Looking at the effects of hallucinogens listed above, one can readily see that the risks/discomfort of hallucinogen use clearly outweigh the benefits.

General Toxic Effects

Although drugs such as ketamine, LSD or MDMA have antidepressant properties, their use is not without adverse consequences. Ketamine has significant

abuse potential and long term use reportedly has toxic effects on the bladder and brain. Other toxic consequences from hallucinogens include overdose signs and symptoms: fever (caused by dehydration and physical exertion) in MDMA (ecstasy) users, sometimes leading to death; high blood pressure and seizure activity; depression and suicidal thoughts after high doses; “bum trips” (an acute anxiety reaction similar to a bad trip with LSD); and even flashbacks. While other effects of MDMA may be mild and self-resolving (e.g., bruxism, headaches, dizziness and nausea) there is evidence that MDMA may produce degeneration of serotonin nerve cells and axons in rats, and possible neurotoxicity in humans. The clinical implications of such findings in humans are not clear.

Mescaline toxicity is characterized by nausea, vomiting, abdominal cramps, diarrhea, sweating, tremor, anxiety, visual and perceptual distortions, and disturbing hallucinations. Toxicities of the other hallucinogens are not as remarkable as those of LSD and MDMA (ecstasy).

Cardiovascular Toxicity

Most hallucinogens produce classic sympathomimetic effects including tachycardia and hypertension. These effects are generally dose-dependent and return to normal after the drug has been metabolized. Hypertensive crises (leading to, for example, intracerebral hemorrhage, cardiac arrest) vary with individual hallucinogens. Methamphetamine and MDMA are associated with cardiac hypertrophy, and sudden death (cardiac failure), whereas mescaline has rather modest effects on the cardiovascular system. High doses actually decrease heart rate. Overall, serious adverse events are low but unpredictable.

Tolerance and Dependence

LSD holds the distinction of having one of the most rapid and dramatic tolerance characteristics of any pharmacological agent. Tolerance does develop to daily doses, and in some cases, a lessening of effect can be seen from one dose to another. Some sources have referred to this as *tachyphylaxis* (rapid tolerance). However, frequent repeated use of LSD is unusual, so tolerance is not commonly seen or well studied. The levels of tolerance seen with other psychedelics are much less dramatic, and in fact tolerance to them is rarely

discussed, either because the use of these drugs is not frequent, or because tolerance is not dramatic.

Likewise, physical dependence and withdrawal from the hallucinogens is not characteristic, nor significant. Whereas the diagnostic manuals do not characterize LSD, MDMA (Ecstasy), and other hallucinogens as producing substance, drug, or chemical dependence (“addiction”), at least one epidemiological study places the lifetime risk for chemical dependence on psychedelics as around 5 percent of users.

Forensic Considerations

As with any drug, severe distortion of reality can result in bizarre responses that may result in criminal behavior or accidental injury. Toxicological testing may be useful in identifying the natures of behavior in a forensic setting. LSD in biological materials is usually analyzed by immunoassay techniques, but the most precise and accurate method for LSD measurement in plasma, whole blood, and urine is via gas chromatography/mass spectrometry (GC/MS). LSD degrades readily in biological specimens unless protected from heat and light. The drug may also bind to glass containers in acid solutions. MDMA can be measured in biological specimens using similar methods to measuring amphetamines (including immunoassay and GC/MS). It is stable in serum, whole blood, and urine for up to 21 weeks at room temperatures or frozen. Mescaline can be determined in biological fluids by fluorometry, GC/MS and liquid chromatography/MS.

Selected Bibliography

- Baselt, R. C. (2008). *Disposition of toxic drugs and chemicals in man*. 8th Edition, Foster City, CA: Biomedical Publications.
- Brunton, L., Chabner, B. and Knollman, B. (2011). *Goodman and Gilman's the pharmacological basis of therapeutics*, 12th Edition, Columbus, OH: McGraw-Hill Companies.
- DeGregorio, D., Aguilar-Valles, A., Preller, K., Dov Heifets, B., Hibicke, M., Mitchell, J. and Gobbi, G. (2021). Hallucinogens in mental health: Preclinical and clinical studies on LSK, psilocybin, MDMA and ketamine. *Journal of Neuroscience*, 41(5): 891–900.
- Erickson, C. K. (2011). *Addiction essentials: The go-to guide for clinicians and patients*. New York: W.W. Norton.

- Hart, C., Ksir, C. and Ray, O. (2010). *Drugs, society, and human behavior*, 14th Edition, Columbus, OH: McGraw-Hill Co.
- Inaba, D. S., Cohen, W. E., von Radics, E. and Cholewa, E. K. (2011). *Uppers, downers, all arounders: Physical and mental effects of psychoactive drugs*, 7th Edition, Medford, OR: P.J. Steinbroner, Publisher.
- Schindler, E. A. D., Dave, K. D., Smolock, E. M., Aloyo, V. J. and Harvey, J. A. (2012). Serotonergic and dopaminergic distinctions in the behavioral pharmacology of (\pm)-1-(2,4-dimethoxy-4-iodophenyl)-2-aminopropane (DOI) and lysergic acid diethylamide (LSD). *Pharmacology Biochemistry and Behavior*, 101: 69–76.
- Tupper, K., Wood, E., Yensen, R. and Johnson, M. (2015). Psychedelic medicine: A re-emerging therapeutic paradigm. *Canadian Medical Association Journal*, 187(14): 1054–1059.
- Wiegand, T., Thai, D. and Benowitz, N. (2008). Medical consequences of the use of hallucinogens: LSD, mescaline, PCP and MDMA (ecstasy). In J. Brick (Ed.), *Handbook of the medical consequences of alcohol and other drugs*. New York: Haworth Press, pp. 461–490.

Nicotine: Of What Value?

15

Tobacco use is world-wide and its presence in architecture (look for tobacco leaves in older federal buildings), in Hollywood and in virtually every convenience store in the country may suggest it is an acceptable product. Why the fuss? One could ask the question: How many more people would have lived longer, productive, happy lives if only we had been able to reduce nicotine use in society sooner? For this is one chemical for which there is no need. Once people begin to use nicotine, it often becomes very difficult for some to stop (i.e., they become “addicted”, or chemically dependent). In spite of early tobacco testimony to the contrary, nicotine is a highly dependence-producing (“addictive”) drug. It takes victims’ lives through lung cancer, heart disease, and emphysema. The scientific evidence for this fact is now so strong as to be irrefutable. Watching old TV commercials in which physicians are portrayed as smokers who recommend certain brands are entertaining until one realizes the seriousness of what they were doing. Today, thanks to extraordinary public pressure, smoking rates in the United States have leveled off, fewer new smokers are lighting up, and taxes on cigarettes have risen to try and protect people too young or not knowledgeable about the dangers of nicotine. Chewed tobacco continues to be a problem in spite of high dependence rates and strong evidence of oral-pharyngeal cancer. This is one drug we wish we didn’t have to cover in this book, except as a historical story.

History of Tobacco Use

Tobacco use dates back to at least the Mayan Indians of Mexico, whose stone drawings show tobacco use (~600–900 AD). Tobacco was grown by American Indians before the discovery of America by Europeans, and they used it for religious and medical purposes. Tobacco was the first crop in North America that was grown for money.

Tobacco is the leading preventable cause of death in the United States. Each year, it causes more than 440,000 deaths, or one of every five deaths in the US, but about 5 million deaths worldwide. About half of regular smokers die prematurely from a tobacco-related disease. In 2021, it was estimated that 12 percent of US adults (age 18 or more) smoked cigarettes (slightly more men than women). While lower than previous study years, that is still about 28 million adults in the US that smoke. In 2022, 27 percent of 12th grade students had vaped nicotine in the last 12 months. Many people continue to smoke in spite of knowing about or experiencing the health consequences of tobacco use. In fact, about half of Americans who smoke, do so even though they have a smoking-related disease. Health problems associated with second-hand smoke (affecting people around the smoker) and thirdhand smoke (harmful toxins that remain after cigarettes are extinguished) have also been documented. Some smokers are able to quit but others cannot, no matter how many attempts are made.

More than 90 percent of adult smokers began smoking when they were teenagers. This is the reason for many recent studies on the dependence potential of nicotine in adolescents, and on methods to reduce smoking in young people. Older, but relevant studies indicate that there is a strong, direct, and independent association between seeing tobacco use in films and trying cigarettes, and that cigarette warning labels are not seen, read, or remembered by “sizable proportions” of adolescent smokers. It appears that even in adults, knowledge of warning labels on cigarette packages and advertisements may not be associated with reduced smoking. In addition, there may be a genetic component to nicotine dependence, which maintains smoking that began in adolescence. Nicotine, along with caffeine is one of the most used legal drugs in the world.

Pharmacokinetics: How Nicotine Gets into the Body

Administration and Distribution

Nicotine is easily absorbed from the respiratory tract, membranes of the mouth, and skin. Severe poisoning has resulted from accidental contact with nicotine on the skin. If ingested, its absorption from the stomach is limited because it is such a strong base (basic pH). Nicotine in chewing tobacco has a longer duration of effect than nicotine through inhalation because it is more slowly absorbed. The average cigarette contains 8–9 mg of nicotine, about 12 percent of which gets into the blood. If the person puffs more enthusiastically or pulls on the cigarette longer, more will reach the bloodstream. Nicotine reaches the brain through the bloodstream in about 10–20 seconds after inhalation. A plug of snuff (smokeless tobacco, chew, “chaw”) kept in the mouth continuously for 30 minutes delivers a dose of about 3–5 mg of nicotine. On the other hand, in e-cigarettes, used to avoid the serious respiratory and cancer causing effects of tobacco, the nicotine-containing vapors are very rapidly absorbed into the circulation.

Cigars are different because generally the smoker does not inhale. Thus, most of the smoke is absorbed in the mouth and upper airways. If a person holds an unlit cigar in the mouth for a long time, generally more nicotine will be absorbed than when someone holds the cigar in a hand and puffs intermittently.

Elimination: How is Nicotine Metabolized and Removed from the Body?

About 80–90 percent of nicotine is changed (metabolized) in the body, mainly in the liver, but some in the kidney and lung. Nicotine is rapidly metabolized primarily by the CYP2A6 isozyme with a half life of about 40 minutes. Cotinine is the major metabolite, with other metabolites found in smaller quantities: about 5 percent of a dose of nicotine is excreted unchanged in the urine, with about 10 percent excreted as cotinine, 35 percent as hydroxycotinine, and about 4 percent as nicotine-1'-N-oxide. Less than 5 percent of a dose is excreted as other known metabolites. Both nicotine and its metabolites are rapidly eliminated in the urine; nicotine is also excreted in the milk of lactating women who smoke.

Pharmacology of Nicotine

Nicotine, the primary ingredient in tobacco, is one of only a few natural liquid alkaloids. It is a colorless, volatile alkaline substance that turns brown and acquires the odor of tobacco on exposure to air. It is classified pharmacologically as a stimulant/depressant of the autonomic ganglia (causing difficult-to-predict effects on heart rate, blood pressure and body secretions). Likewise, in the central nervous system it produces both stimulation and depression of mood, calming the smoker who feels anxious when not smoking, and stimulating the person who wants to work longer and harder. Its initial effect on non-smokers is stimulation of the central nervous system, leading to tremors, sometimes convulsions, increased respiration, and vomiting. Extreme stimulation may be followed by depression of respiration and death. Nicotine has at various times been used as an animal tranquilizer, because of its effects on blocking muscle contraction, and an insecticide – one of the most potent available.

Pharmacodynamics

Nicotine increases brain activity in the prefrontal cortex, thalamus, and visual system and because it is structurally similar to the neurotransmitter acetylcholine, stimulates nAChRs nicotine receptors. The nAChRs receptors are ligand-gated ion channels. When a cholinergic agonist (in this case nicotine) binds to the receptor, the channel opens allowing sodium and calcium to enter the cell and causing depolarization. This causes the release a range of neurotransmitters but most notably dopamine. The release of dopamine in the ventral tegmental area of the midbrain and nucleus accumbens, both of which are part of the brain reward pathway explains the highly addictive nature of nicotine. Like other psychoactive drugs, nicotine also stimulates the release of GABA and serotonin.

Nicotine might increase memory, based upon its effects of increasing nerve cell activity in brain structures associated with memory. Other brain areas such as those involved with mental functioning and muscle movement are also affected. Indeed, nicotine has been used in studies of Alzheimer's patients to increase memory and mental function. While synthetic drugs that mimic nicotine's action might some day help Alzheimer's patients, this effect is likely to be subtle and certainly not a cure for the disease but it is an opportunity to introduce other medical problems.

Tolerance and Dependence

Some reports have placed the number of smokers who become chemically dependent on nicotine at about 32 percent, the highest of all drugs (note that this is not the same as physical dependence, which relates to withdrawal from nicotine, that may or may not occur in chemically dependent nicotine users). Nicotine certainly causes withdrawal symptoms in many people who try to stop. Tolerance occurs to the initial effects of smoking, so that more and more tobacco is necessary to satisfy the smoker. Most people, however, can stop smoking once they make a decision to stop. Most of these people try “cold turkey” (stopping without any tapering of the nicotine dose). Some people who were once heavy smokers now report that they were able to stop with no problem and “don’t even think about nicotine anymore”. (Such smokers are not “addicted”.) The ease of chemical dependence production and the extreme difficulty in stopping seen in many smokers place nicotine among the top in any list of “addicting” drugs. The fact that this occurs with a drug that produces nowhere near the euphoric power of drugs such as cocaine and morphine tells us that the “high” or sense of well-being produced by a drug is not the main cause of chemical dependence.

Some people have such a severe form of nicotine dependence that they will continue to smoke even while hooked up to a mobile oxygen tank, or immediately after coronary by-pass surgery. These individuals will usually die of lung cancer or heart disease. There are several smoking cessation aids on the market, including the skin patch (NicoDerm) and nicotine chewing gum (Nicorette). Nicotine nasal sprays, a nicotine inhaler, and low nicotine non-smoking devices are also available as nicotine replacement therapies (NRTs). These have helped many people but a recent study has suggested the NRTs may not be as effective as previously believed. Surely, NRTs alone may not be very effective in reducing smoking. As always, ongoing counseling to help the smoker stop is required. NRTs may only be useful, when used properly, to reduce the severity of withdrawal, the signs and symptoms of which are listed in Table 15.1.

Bupropion (Zyban) can be used as part of a smoking cessation program. Bupropion is an antidepressant medication that reduces the depression associated with getting off nicotine. Tapering the nicotine through self-reduction using the gum or patch, when combined with bupropion, can be very effective for some people. For others, hypnosis, counseling and/or a strong motivation to stop is sufficient. A new innovation, now in clinical

Table 15.1 Signs and Symptoms of Nicotine Withdrawal

-
- Intense craving for nicotine
 - Anxiety, tension, restlessness
 - Frustration, impatience, and/or irritability
 - Difficulty concentrating
 - Drowsiness or trouble sleeping (sometimes bad dreams)
 - Headaches
 - Increased appetite and weight gain
 - Depression
-

These generally begin 2–3 hours after last tobacco use and vary in number and intensity between individuals.

studies, is a nicotine vaccine that blocks the drug from entering the brain and is designed to be used in conjunction with counseling and other cessation strategies. The best advice for someone who wants to stop smoking is to try “cold turkey”, and if more motivation is needed, to seek the advice of a smoking cessation professional (some physicians, psychologists or others). For some people resistant to cold turkey or other measures, bupropion is their savior. For others, a new medication called varenicline (Chantix) works better. Of course, what works for one person might not work for another.

A relatively new observation is that nicotine replacement therapy methods are used by adolescent and adult smokers *and* non-smokers. They are readily accessible, and are used for reasons other than trying to quit smoking. Many smokers who switch to patches (for example) will continue to use the patches, while claiming that they are “better off” than if they had continued to smoke cigarettes every day. While they may be relieved of the long-term effects of tars, carbon monoxide, and smoke ingredients that are carcinogenic, many pharmacologists believe that nicotine itself can produce serious effects on the heart.

Medical Consequences of Nicotine and Tobacco Use

It has been known for decades that the use of nicotine creates dependence and continued smoking leading to a multitude of health problems including heart disease, lung disease, cancer and increased susceptibility to infections. The use of tobacco as a vehicle to transport nicotine harms virtually every organ in the body. The accidental ingestion of insecticide sprays containing nicotine, or the ingestion of tobacco products by small children, can lead to

poisoning (although this is rare these days). The acute fatal dose of nicotine for an adult is probably about 40–60 mg of pure nicotine; for children, much less. In one cigarette, about 0.2–2.4 mg of nicotine survive combustion.

The onset of symptoms of acute, severe nicotine poisoning is rapid. Symptoms include nausea, salivation, abdominal pain, vomiting, diarrhea, cold sweats, headache, dizziness, hearing and vision problems, mental confusion and marked weakness. After these symptoms, there are faintness and tiredness; a fall in blood pressure; difficulty in breathing; weak, rapid and irregular pulse; and collapse followed by convulsions ending in death. Death may result within a few minutes of respiratory failure.

The ingestion of cigarettes or used transdermal patches by children can lead to cases of nonfatal poisoning. Toxicity has also been seen in tobacco harvesters, probably as a result of absorption of nicotine through the skin.

When nicotine is ingested, the induction of vomiting can be very helpful in overcoming acute nicotine poisoning, presumably because nicotine from tobacco taken by mouth slows the emptying time of the stomach. (Intestinal absorption of nicotine is more efficient than absorption through the stomach.) Treatment involves inducing vomiting with syrup of ipecac. Another effective treatment is gastric lavage, preferably followed by a slurry of activated charcoal left in the stomach. If necessary, artificial respiration and treatment of shock should be initiated.

Finally, there are age-related consequences from smoking tobacco. Most people start smoking early in life and at a time that the frontal cortex is still developing. Teenagers are by their very nature, somewhat impulsive and particularly influenced by their peers. Experimenting with cigarettes is a common early exposure to nicotine, a highly addictive drug. It cannot be overemphasized that among scientists, there is no question that smoking has a host of serious medical consequences including cardiovascular disease and cancer.

Forensic Considerations

Although nicotine is toxic, only a few cases of nicotine-induced deaths have been reported. For example, postmortem blood concentrations of 11–63 mg/L (average, 29) were seen in five adult subjects who swallowed 20–25 grams of nicotine sulfate solution. They died within one hour. Other fatal cases have involved blood nicotine concentrations that reached as high as 600 mg/L. In

1967, nicotine was a major drug used in suicides in Hungary. A more recent study suggested that there may be an increased use of cigarettes in individuals contemplating suicide. High (>6 percent) carbon monoxide (carboxy hemoglobin) concentration of more than 6 percent in blood suggest recent exposure to concentrations of smoke. In the absence of nicotine or nicotine metabolites in blood, this may be of importance in some death cases. Finally, a case study described a man who continued to smoke while wearing several transdermal nicotine patches. He suffered cardiac arrest, and died four days later in the hospital. Pharmacokinetic and pharmacodynamic drug effects should always be evaluated on a case-by-case basis.

Selected Bibliography

- Baselt, R. C. (2008). *Disposition of toxic drugs and chemicals in man*, 8th Edition, Foster City, CA: Biomedical Publications.
- Benowitz, N. (2009). Pharmacology of nicotine addiction, smoking-induced disease and therapeutics. *Annual Review of Pharmacology and Toxicology*, 49: 57–71.
- Blondal, T., Franzon, M. and Westin, A. (1997). A double-blind randomized trial of nicotine nasal spray as an aid in smoking cessation. *European Respiratory Journal*, 10: 1585–1590.
- Breslau, N., Johnson, E. O., Hiripi, E. and Kessler, R. (2001). Nicotine dependence in the United States: Prevalence, trends, and smoking persistence. *Archives of General Psychiatry*, 58: 810–816.
- Dani, J. A. (2003). Roles of dopamine signaling in nicotine addiction. *Molecular Psychiatry*, 8: 255–256.
- Dani, J. A. and De Biasi, M. (2001). Cellular mechanisms of nicotine addiction. *Pharmacology Biochemistry and Behavior*, 70: 439–446.
- Foulds, J., Delnevo, C., Ziedonis, D. and Steinberg, M. (2008). Health effects of tobacco, nicotine, and exposure to tobacco smoke pollution, in Brick, J. *Handbook of the medical consequences of alcohol and drug abuse*, 2nd Edition, New York: Haworth Press, pp. 423–460.
- Jaffe, J. (2020). *Making the case for nicotine addiction: Selective reminiscences: A commentary on Kozlowski, et al. Journal of Studies on Alcohol and Drugs*, 81(6): 738–739.
- Klesges, L. M., Johnson, K. C., Somes, G., Zbikowski, S. and Robinson, L. (2003). Use of nicotine replacement therapy in adolescent smokers and nonsmokers. *Archives of Pediatric and Adolescent Medicine*, 157: 517–522.
- Mansvelder, H. D., De Rover, M., McGehee, D. S. and Brussaard, A. B. (2003). Cholinergic modulation of dopaminergic reward areas: Upstream and downstream targets of nicotine addiction. *European Journal of Pharmacology*, 480: 117–123.
- Moriya, F. and Hashimoto, Y. (2004). Nicotine and cotinine levels in blood and urine from forensic autopsy cases. *Legal Medicine*, 6: 164–169.

- Munafo, M., Johnstone, E., Murphy, M. and Walton, R. (2001). New directions in the genetic mechanisms underlying nicotine addiction. *Addiction Biology*, 6: 109–117.
- Pentel, P. and Malin, D. (2002). A vaccine for nicotine dependence: Targeting the drug rather than the brain. *Respiration*, 69: 193–197.
- Rigotti, N. A. (2002). Treatment of tobacco use and dependence. *New England Journal of Medicine*, 346: 506–512.
- Robinson, T. N. and Killen, J. D. (1997). Do cigarette warning labels reduce smoking? *Archives of Pediatric and Adolescent Medicine*, 151: 267–272.
- Sargent, J. D., Beach, M. L., Dalton, M. A., Mott, L. A., Tickle, J. J., Ahrens, M. B. and Heatherton, T. F. (2001). Effect of seeing tobacco use in films on trying smoking among adolescents: Cross sectional study. *British Medical Journal*, 323: 1394–1397.
- Schuh, K. J., Schuh, L. M., Henningfield, J. E. and Stitzer, M. L. (1997). Nicotine nasal spray and vapor inhaler: Abuse liability assessment. *Psychopharmacology*, 130: 352–361.

Addiction: The Chronic Medical Illness 16

The field of addiction has no shortage of theories about the causes of drug use or addiction as evidenced by a number of catch-all terms such as the “biopsychosocioeconomic” basis for drug abuse. In the search to explain complex phenomena, theorists have tended to either generalize or overly molecularize. For example, drugs were considered addicting only if they produced physical withdrawal signs upon discontinuation of use. Not that long ago, many people believed anything that you love or makes you feel good can be addicting (chocolate, caffeine, sex, nicotine, cellphones). In fact, the term “addiction” has lost its scientific meaning over the years. Clinicians and scientists now use more precise, less emotion-laden terminology to describe the condition of an “inability to stop using a drug.” We’re not talking about “not wanting to stop”; rather, we’re describing a disease state in which the patient cannot stop using a drug, even when the desire to stop is strong. The focus of DBB is on the physiological substrates of behavior. We believe strongly that while social and interpersonal factors contribute to drug use disorders, addiction is a disease state caused by a brain chemistry imbalance in a part of the brain known as the “pleasure (or reward) pathway”. In this chapter, we will review some historical and current definitions and features of addiction and discuss how reward pathway neurochemical dysregulation fits with current clinical definitions of addiction.

Definitions

Major misunderstandings exist among professionals and the general public about the definitions of terms such as addiction, chemical dependence,

substance abuse, physiological dependence and drug misuse (See Chapter 1). It is not surprising that such a complex field has created misunderstandings. Many people are confused by the abuse and dependence classifications, because they still remember the old definition of addiction formulated by the World Health Organization (WHO) in 1950. This old definition stated that “addicting drugs” had three qualities: (1) psychological dependence (roughly, habituation or “craving”), (2) tolerance (adaptation to the drug so that more and more is needed to produce the original effect), and (3) physical dependence (adaptation of the body to the drug so that one can only function normally when the drug is present). While this definition properly describes “addiction” to central nervous system drugs such as heroin and alcohol, it falls short of describing “addiction” to other drugs, such as cocaine that has no significant physical withdrawal. For example, in the case of cocaine, up to 95 percent of withdrawal is emotional, rather than physical. Even today, some argue that cocaine is not addictive because of this lack of physical withdrawal – a dangerous and uneducated argument.

A key component of addiction continues to be “impaired control” over drug use and the concept of dependence (addiction) has both psychological and physical characteristics. “Impaired control” is an obsessive preoccupation with the use of the drug (psychological), and the primary cause of impaired control is a neurochemical (physical) dysregulation (something gone wrong) in the brain. Impaired control is what is seen, but neurochemistry is what is happening. An attempt to differentiate between physical and psychological addiction has no value today except to simplify a very complex disease. The use of psychoactive drugs for their pleasurable effects (initial acute use) or the complete loss of control with severe substance use disorder (SUD) (evidenced by chronic uncontrolled use), is neurochemical in nature. Social or environmental factors and psychoactive drugs only affect behavior by altering brain neurochemistry. As stressed throughout all editions of DBB, drugs do not get you high – changes in brain chemistry get you high. Similarly, it is the same change in neurochemistry that causes addiction. To still argue, as some do, that addiction is not a brain disease not only fails to understand current neuroscientific thinking but do a disservice to patients. As a disease addiction may be covered by insurance, the stigma of what on what may superficially appear to be a moral weakness or bad choices reduced whereas believing that addiction is a matter of choice does not.

Finally, even though we use the term addiction in the chapter title and throughout this book it is not a very precise term. It is just so embedded in

vocabulary that it is unlikely to go away. Are we addicted to our cell phones because we use them incessantly and feel uneasy if we forget our phone when we leave home? Are we addicted if our craving for a drug gets so out of control that we do things that place us in danger? Everyone knows what it means to say you are addicted to coffee (caffeine), a television show or some similar repetitive, time sink, pre-occupying “thing” but as my colleague Carl Erickson has often said, the term is too broad, imprecise, non-scientific. Clinicians who helped guide the latest diagnostic manual for addictive disorders and other mental illnesses (see below) considered some of these everyday addictions and found insufficient scientific evidence of behavioral addictions to sex, exercise, shopping, the Internet, etc. The best we can do is realize that addiction to a drug is very different from the above somewhat compulsive behaviors.

Current Terminology

The *Diagnostic and Statistical Manual of Mental Disorders* (known as the DSM), is published by the American Psychiatric Association. The DSM is the clinicians go-to text to diagnose mental disorders and is updated regularly, based upon new clinical and research information. The current fifth edition (DSM-5) has revised previous definitions and criteria in the field of alcohol and drug abuse and dependence. The major differences between older and current diagnostic terminology are: (1) all substance use disorders are now combined into a single diagnostic category termed, substance use disorder (SUD) and not two categories: abuse and dependence; (2) there are now three categories of SUD severity (more than previously required); (3) non-drug “addictions” are recognized but the only “behavioral (process) addiction” that is currently included is gambling. Terms such as “Internet addiction” are listed in the appendix of DSM-5 but not included elsewhere.

Substance use disorders can be characterized as: (1) at risk; (2) mild; (3), moderate; or (4) severe based on the number of criteria (Table 16.2).

- One criteria could indicate an individual is at risk
- Two or three criteria point to a mild substance use disorder
- Four or five criteria show someone has a moderate substance use disorder
- Six or more criteria indicate a severe substance use disorder, which signals an addiction to that substance

Table 16.1 DSM -5 Criteria for Substance Use Disorder

1. Using more of a substance than intended or using it for longer than you're meant to
2. Trying to cut down or stop using the substance but being unable to
3. Experiencing intense cravings or urges to use the substance
4. Needing more of the substance to get the desired effect – also called tolerance
5. Developing withdrawal symptoms when not using the substance
6. Spending more time getting and using drugs and recovering from substance use
7. Neglecting responsibilities at home, work or school because of substance use
8. Continuing to use even when it causes relationship problems
9. Giving up important or desirable social or recreational activities due to substance use
10. Using substances in risky settings that put you in danger
11. Continuing to use despite the substance causing problems to your physical and mental health

Signs of withdrawal are summarized in Table 16.2. There remains insufficient research on other process addictions; thus, the following terms will continue to be scientifically inappropriate and colloquial (in everyday lay language): food addiction, sex addiction, exercise addiction, cosmetic surgery addiction, addiction to oil, suntan booth addiction, lingerie addiction, jelly bean addiction, Facebook addiction, religion addiction, etc. None of these produce signs or symptoms as described in Table 16.2

Neurochemical Dysregulation as a Cause of Addictions

Neuroscientists who study the brain now believe that the site of action of all addicting drugs probably lies within the mesolimbic dopamine system (MDS, pleasure or reward pathway) of the brain, where our instinctual drives and ability to experience emotions and pleasure reside (see Figure 16.1). Another anatomical name for the MDS is the medial forebrain bundle. The MDS runs from the center of the brain (in an area known as the ventral tegmental area, through a major “relay station” known as the nucleus accumbens, and up to the front part of the brain, known as the frontal cortex. These areas, as well as several other nerve pathways that feed into them, have been well documented in animals. Seven major neurotransmitters are involved in the response to

Table 16.2 DSM-5 Symptoms of Withdrawal*

Substance	Symptom or Sign
Alcohol	Two or more of the following: (1) autonomic hyperactivity; (2) increased hand tremor; (3) insomnia; (4) nausea or vomiting; (5) transient visual, tactile or auditory hallucinations or illusions; (6) psychomotor agitation; (7) anxiety; (8) generalized tonic-clonic seizures
Cannabis	Three or more of the following: (1) irritability, anger or aggression; (2) nervousness or anxiety; (3) sleep difficulty (e.g., insomnia, disturbing dreams); (4) decreased appetite or weight loss; (5) restlessness; (6) depressed mood; (7) at least one of the following physical symptoms causing significant discomfort: abdominal pain, shakiness/tremors, sweating, fever, chills or headache
Stimulant Use	Dysphoric mood and two or more of the following: (1) fatigue; (2) vivid, unpleasant dreams; (3) insomnia or hypersomnia; (4) increased appetite; (5) psychomotor retardation or agitation
Hallucinogens and Phencyclidine	No withdrawal diagnosis
Inhalants	No withdrawal diagnosis
Opioids	Three or more of the following: (1) dysmorphic mood; (2) nausea or vomiting; (3) muscle aches; (4) lacrimation or rhinorrhea; (5) yawning; (6) pupillary dilation, piloerection or sweating; (7) diarrhea; (8) fever; (9) insomnia
Sedative, Hypnotic or Anxiolytic	Two or more of the following: (1) autonomic hyperactivity; (2) hand tremor; (3) insomnia; (4) nausea or vomiting; (5) transient visual, tactile or auditory hallucinations or illusions; (6) psychomotor agitation; (7) anxiety; (8) grand mal seizures
Tobacco	Four or more of the following: (1) irritability, frustration or anger; (2) anxiety; (3) difficulty concentrating; (4) increased appetite; (5) restlessness; (6) depressed mood; (7) insomnia
Other substance	A syndrome of substance-specific symptoms that causes clinically significant distress or impairment in social, occupational or other areas of functioning

*Although technically incorrect, DSM continues to use the term symptoms to describe both signs and symptoms.

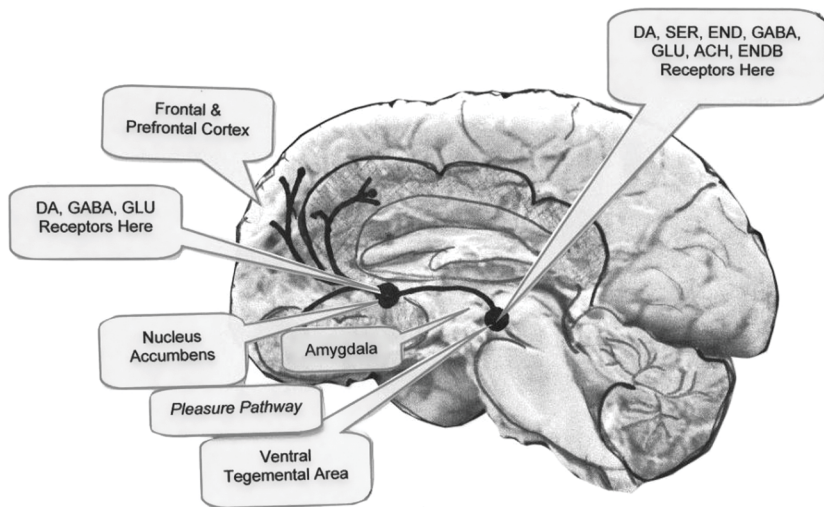


Figure 16.1 Mesolimbic dopamine system (MDS)

drugs and the transmission in the MDS pleasure pathway. In Figure 16.1, the receptors in the upper right corner of the figure are places where specific drugs act to activate this pathway:

- Dopamine (DA) – cocaine, amphetamines, alcohol
- Serotonin (SER) – LSD, alcohol
- Endorphins (END) – opioids, alcohol
- GABA – benzodiazepines, alcohol
- Glutamate (GLU) – alcohol
- Acetylcholine (ACH) – nicotine, alcohol
- Endocannabinoids (ENDB) – marijuana, alcohol

When the individual drugs activate receptors at the places indicated, they cause the pleasure pathway to carry messages of “pleasure”. When dysregulation of the pathway occurs (meaning there is a problem with neurotransmitter or receptor function), this is the basic cause of chemical dependence (“addiction”). The impaired use of the drug (the main symptom of the disease) is related to dysregulation of one or more neurotransmitter systems, leading a person to use that drug in an attempt to “re-regulate” the pathway. This is postulated to be why people have “drugs of choice” and why the drug of choice is determined by the neurotransmitter system that is dysregulated.

Thus, a person whose drug of choice is heroin presumably has a dysregulation of the endogenous opioid system and a person with more than one drug of choice is presumed to have dysregulation of more than one neurotransmitter system. Note that alcohol, a very “dirty” drug pharmacologically (it affects multiple neurotransmitter systems), presumably can cause dependence (“addiction”) through the dysregulation of all the listed pathways.

Regardless of the complexity of the reward pathway as it unfolds in continuing studies in neuroscience laboratories, scientists now believe that all drugs and social experiences that produce pleasure act on this pathway. In particular, drugs such as heroin, alcohol, and nicotine are known to act at least partially on the ventral tegmental area to produce euphoria. Drugs acting on the nucleus accumbens include cocaine, alcohol, and benzodiazepines. These probable sites of drug action have been found in animal studies within the past two decades, and are continually being refined and updated with new research.

Other Hypotheses About “Addiction”

All of the drugs discussed in this book produce euphoria and craving. But many clinicians believe that euphoria and craving alone are insufficient to produce the impaired control over drug use that characterizes “addiction”, or chemical dependence (older DSM-IV terminology) or drug use disorders (DSM-V). One hypothesis suggests that “like-want” pathways in the MDS are intimately involved in the tolerance to euphoria and the enhanced craving that occurs in a chronic drug user. While this hypothesis provides an interesting explanation of the causes of drug misuse and overuse, it has been speculated that the MDS will soon be found to include another functional pathway, termed the “need” pathway. This need pathway could be active, because of neurochemical dysregulation, in the drug addict who cannot stop using the drug in spite of adverse consequences. The instinctual need for the drug explains the impaired control, since the person perceives the drug as intimately connected with existence, much like breathing, thirst, hunger and the drive for sex. Thus, when drug users report they “can’t stop” drinking or drugging, they really can’t stop without mutual-group or professional help. Many alcoholics and other chemically-dependent people truly want to stop, but cannot do so on their own. In general, those with alcohol or other SUDs will stop when they feel that life events or consequences of drinking or using

are too overwhelming, and that they would be better off as social users or abstainers.

In a psychiatric sense, chemical dependencies may be nothing more than sophisticated obsessive-compulsive disorders because clinicians can see behavior directed at particular favorite agents: alcohol, sex, food, gambling, overwork, cocaine, nicotine, etc. Some scientists like this idea, since the negative public attitude toward drug addicts and alcoholics is so severe that funding for treatment, research, education, and prevention of these drug-induced diseases is miserably deficient. When people stop blaming the drug-afflicted for their disease by shifting the emphasis from the blame of drug use to a brain-chemistry dysregulation causing an inability to stop drug use, perhaps public sympathy will produce a realistic movement to help those individuals afflicted and suffering with these diseases. But it will take time.

Treatment of Addictions

Drugs, The Brain and Behavior focuses on the pharmacology of therapeutics, drug use and drug use disorders. Nevertheless, focusing only on the pharmacology without structured behavioral treatment would be short-sighted and ignore the contribution of clinical behavioral treatments. For example, problem drug users generally reduce their drug use when they respond to counseling, adverse life events, changes in lifestyle, and education about the detrimental effects of drugs and treatment goals.

The traditional talk therapy consists of 12-step (anonymous) programs that have been in existence since the mid-1930s. These are highly effective (for some) mutual-help programs that encourage problem drug users find lifetime abstinence from drugs of choice and other “addicting” drugs and behaviors. The most popular of these is Alcoholics Anonymous (AA), but Narcotics Anonymous (NA) is also popular, as well as other 12-step programs for smoking, overeating and other compulsive behaviors. There has been sufficient research on Alcoholics Anonymous programs over the past twenty years so that some scientists have declared A.A. to be an “evidence-based” (research-proven) treatment component.

Twelve-step programs are the foundation of most effective inpatient and outpatient programs today. In established high-end inpatient treatment centers, the emphasis is on complete assessment and diagnosis of co-occurring mental, physical, legal, financial and relationship problems, followed by

individual and group counseling, a healthy diet and recreational lifestyle, education about the disease and follow-up aftercare once formal treatment ends. Most experts in the field now realize that chemical dependence is a chronic, relapsing disease that did not occur overnight, and that the longer a person remains in formal treatment and aftercare programs, the better outcome there will be.

Other forms of therapy are also useful and it is clear from treatment of various SUDs that a combination of medications that reduce drug use with talk-therapy or other behavioral approaches is more effective than a single form of treatment. For example, the Harm Reduction model seek to reduce the harmful effects of SUDs by reducing rather than eliminating drug use. In some user's total abstinence is not a realistic goal at the start of their treatment or for that person. In such instances, the treatment goal is to reduce use and reduce harm. For example, encouraging one bag of heroin, not three per day, providing sterile syringes and directly engaging with people to prevent overdose, disease transmission and improving physical and mental health. Given the fact that in 2022 there were about 100,000 drug-involved overdose deaths, this approach clearly has potential value. However, there are concerns that providing crack-pipes, syringes, etc. may encourage drug use. Also, harm reduction programs do not reach the groups most in need. Another approach to reducing substance use views behavior as a pattern of responses and for some, that response is drug use. The Behavioral Allocation Disorder views addiction as behavioral problem in which drug use is a rapid and "automatic" response rather than a slower deliberative process. The Behavioral Allocation Disorder approach emphasizes therapies that help the individual to focus on allocating behavior towards non-drug solutions.

Because chemical dependence is a medical disease that deserves the same level of health professional attention as the physical diseases such as cancer, heart disease, and diabetes, high-end treatment centers either include detox facilities or are connected to health centers with such facilities. Likewise, medical staff (including physicians and nurses), social workers, and mental health or chemical dependence counselors are mainstays of facilities that are most effective in treating this disease in the long-term. Many facilities and addiction medicine specialists are now depending more and more on anti-relapse (abstinence-enhancing) medications such as those shown in Table 16.3.

There are some important implications and guidelines involved with the use of medications for the treatment of chemical dependencies. First, these medications are not magic bullets that will, when taken, stop alcohol

Table 16.3 Common Medications to Treat Chemical Dependencies

Used for Treatment of:	Medication	Common Names	Mechanism of Action
Alcohol dependence	acamprosate	Campral	Partial co-agonist that normalizes NMDA receptors and other neurochemical systems
	disulfiram	Antabuse	Blocks the metabolism of aversive toxic acetaldehyde
	naltrexone	Revia	Opioid antagonist
	ondansetron	Zofran	SSRI antagonist
Opioid dependence	topiramate	Topamax	Decreases depolarization by blocking Na-gated channels and enhances GABA activity
	buprenorphine	Suboxone	Opioid agonist (buprenorphine) and antagonist (naloxone)
	methadone	Generic	Opioid agonist
Nicotine dependence	naltrexone	Revia+	Opioid antagonist
	bupropion	Zyban	NE/DA Reupdate inhibitor
	varenicline	Chantrix	Nicotinic receptor antagonist
Nicotine	replacements	Various skin patches, nasal sprays, lozenges	Partial nicotinic acetylcholine receptor agonist

or other drug use. Second, they do not work for the treatment of problem drug use except chemical dependence. Third, they should not be used unless the patient is also involved in an abstinence-based treatment program, counseling, or a 12-step program. Fourth, these medications will work for only about (on an average) half of the patients who take them. More medications are urgently needed for treating people with other chemical dependencies (cocaine, amphetamine, benzodiazepine and other dependence-producing drugs covered in earlier chapters). Finally, for full utilization of medications and other treatments/programs described above, the medical professions

(medicine, nursing, dentistry, pharmacy) must begin to include the teaching of addiction medicine to their practitioners. Depending upon counselors and other non-medical treatment professionals to shoulder the burden of treating patients with such life-threatening chronic conditions is not only unfair, but it runs counter to the growing body of research and clinical evidence that these are medically-treatable brain diseases.

Physiological but Non-pharmacological Factors in Relapse

Some aspects of euphoria, craving, or even tolerance may have a non-pharmacological component involving learning. For example, cocaine and nicotine have been shown to strengthen neural connections through a process called long term potentiation (LTP). The LTP of neuron activity that occurs during the learning process is believed to be important in making associations (learning and memory). The use of cannabis increases and decreases LTP, depending upon the brain region; morphine inhibits LTP in neurons that inhibit GABA pathways; and alcohol disrupts LTP. Why is this relevant? Because the pairing of environmental cues associated with drugs (people, places and things) can cause physiological and psychological effects similar to the drug, even when the drug is not present. For example, regular use of a drug in a particular environment or with certain people can create strong cognitive connections associated with drug use. Such cues become conditioned stimuli so that the presentation of the conditioned stimulus tricks the brain into responding as though the drug were present. Exposure to such cues during abstinence makes it more likely that the “addicted” person will relapse. Thus, the “people, places and things” concept in Alcoholics Anonymous probably has a scientific basis.

Conclusions

Neuroscientists and geneticists now believe that the neurochemical problem in addictions is best described as a chemical dysregulation (some chemical system is not working properly) in one or more parts of the brain reward system. Thus, we can think of addictions as chemically dysregulated diseases, much like Parkinsonism (caused by insufficient DA in a part of the brain)

and diabetes, in which there is a lack of proper insulin release in the pancreas. However, we now know that addictions are much more complicated, involving dysregulations in at least seven MDS neurochemical systems. Since these neurochemical systems are those used by drugs to produce their characteristic pharmacological effects, it appears as if “drugs-of-choice” are related to dysregulations in individual neurotransmitter systems utilized by each drug. For example, a person with an opioid use disorder (“opioid addict”) is postulated to have a dysregulation of the endogenous opioid system.

Addiction sciences are telling us that chemical dependence (addiction) is a disease over which the individual has impaired control. The disease process is best characterized as a brain chemistry-dysregulation disorder, which will some day yield to much more cost-effective and specific therapies for addictions than those available today. Drug use including abuse is a behavioral problem that responds to coercion, education and decreased availability, whereas SUD addictions require intensive multidimensional therapies that will soon include, and perhaps one day be replaced by, medications and other therapies discovered through new methods in neuropharmacology. In the meantime, new brain imaging studies are showing that currently-available “talk therapies” (including 12-step programs) help many drug abusers and chemically dependent individuals by changing brain function. It is not surprising that counseling, other talk therapies, and medications act similarly in treating “addictions”, to overcome neurochemical dysregulation and to move the brain chemistry back towards normal.

Looking Ahead

Scientists and clinicians working in the field know first-hand the many problems that stem from addiction and there is much more work to be done in this field. However, there is cause for optimism that we will eventually prevent drug and alcohol disorders and their harmful consequences. The reason for such optimism is because everything we already know and all that we will eventually learn about the pharmacology and therapeutics of drug use disorders comes from our brain – not just because we think and work hard towards a solution but because the answer is literally in our brain. If you look at the big picture, the answer is complex. It is very complex. We all have about 80 billion neurons each connected to thousands of other neurons, each talking through the process of neurotransmission of more than 60 different

excitatory or inhibitory neurotransmitters released into trillions of synapses, interacting with dozens of specific receptors and subsets of receptors to either release or inhibit the release of one or more of those neurotransmitters. This process takes place millions of times a second, every moment of our life. To say it is complex is an understatement but that process is the basis for our behavior.

However, on the molecular level, the neurochemistry of the individual neurons that make up the brain is by comparison, simple. Neurons polarize and depolarize and neurochemicals are released or not released and the dance of convergence and divergence goes on repeatedly. In thinking about solving the puzzle of addiction one might begin with the question, why are some people more susceptible to drug use and dependence whereas others are resilient? What makes us different when in fact we likely have similar desires or expectations? The biological basis of subjective feelings of joy, exhilaration, love, optimism, and so much more is clearly related to specific receptors and brain pathways that make us feel good, help to relax or motivate us. The fact is that initially people take drugs that affect those receptors and brain pathways to experience, joy, happiness, relaxation or stimulation, no matter how short-lived.

One of the greatest discoveries in neuroscience is that our brain (and other parts of our body) has specific receptors for psychoactive drugs that produce these subjective feelings. Whether it is a prescribed therapeutic medication or an illegal drug of abuse, stimulants initially make us feel better, alert, exhilarated, optimistic and full of energy whereas depressants have a completely different effect. Those drugs exert their effects through the same neural pathways the brain uses to produce those feelings without drugs. This begs the question, why do we have receptors in our brain that are so specifically matched to and respond to psychoactive drugs? What is the purpose? Is it a coincidence that we have receptors specifically sensitive to benzodiazepines, opioids and cannabinoids? The answer to that question is there are no coincidences.

We now know that the brain manufactures its own “drugs” in the form of endogenous opioids, cannabinoids and benzodiazepines and many neurotransmitters such as norepinephrine or serotonin have a remarkably similar structure to other drugs such as amphetamines and various hallucinogens. In other words, theoretically we should experience the benefits of stimulating the brain without the use of chemicals from the outside world. Many people are naturally happy, stress-free and relaxed whereas others are

driven sometimes to the point of a disorder or look to outside sources to be relaxed or stress-free.

Most of what we need is endogenous. It is in our brain. Sometimes, our brain does not work and we become ill and in other cases, we may be in pain and our brain releases endogenous opioids to calm our pain or in periods of stress, the release of norepinephrine in the brain and pituitary hormones that stimulate the release of adrenaline energize us to respond to a threat. In other cases, psychotherapeutic medications help normalize brain function or we seek drugs to change our brain chemistry to find pleasure or distraction. Perhaps we need to find other activities or ways to get those changes going. As we learn and understand more about how our brain works, scientists can develop treatments that change the brain and change behavior. Together, psychology and pharmacology are working towards solutions to help chemically-dependent patients live happy, joyous and free from addiction!

Selected Bibliography

- American Psychiatric Association (2013). *Diagnostic and statistical manual of mental disorders*, 5th edition. (DSM-V). Washington, DC: American Psychiatric Association.
- American Psychiatric Association (2000). *Diagnostic and statistical manual of mental disorders*, 4th edition, text revision. (DSM-IV-TR). Washington, DC: American Psychiatric Association.
- American Psychiatric Association (1994). *Diagnostic and statistical manual of mental disorders*, 4th edition. (DSM-IV). Washington, DC: American Psychiatric Association.
- Brick, J. (1990). Learning and motivational factors in alcohol consumption. In: W. M. Cox (Ed.), *Why people drink: Parameters of alcohol as a reinforcer*. Gardner Press, pp. 169–192.
- Center for Behavioral Health Statistics and Quality (2016). *Impact of the DSM-IV to DSM-5 Changes on the National Survey on Drug Use and Health. Substance Abuse and Mental Health Services. Impact of the DSM-IV to DSM-5 Changes on the National Survey on Drug Use and Health. Substance Abuse and Mental Health Services Administration Center for Behavioral Health Statistics and Quality* Rockville, Maryland 20857.
- Dengenhardt, L., Webb, P., Colledge-Frisby, S., et al. (2023). Epidemiology of injecting drug use, prevalence of injecting-related harm, and exposure to behavioural and environmental risks among people who inject drugs: A systematic review. *Lancet Global Health*, [https://doi.org/10.1016/S2214-109X\(23\)00057-8](https://doi.org/10.1016/S2214-109X(23)00057-8)
- Diagnostic and statistical manual of mental disorders*, 5th Edition: DSM 5. American Psychiatric Association.

- Erickson, C. K. (2007). *The science of addiction: From neurobiology to treatment*. New York: W.W. Norton.
- Erickson, C. K. (1992). A pharmacologist's opinion. Alcoholism: The disease debate needs to stop. *Alcohol and Alcoholism*, 4: 325–328.
- George, D. T., Gilman, J., Hersh, J., Thorsell, A., Herion, D. et al. (2008). Neurokinin 1 receptor antagonism as a possible therapy for alcoholism. *Science*, 319: 1536–1539.
- Gould, T. (2010). Addiction and cognition. *Addiction Science Clinical Practice*, 5(2): 4–14.
- Grant, B. F., Dawson, D. A., Stinson, F. S., Chou, S. P., Dufour, M. C. and Pickering, R. P. (2004). The 12-month prevalence and trends in DSM-IV alcohol abuse and dependence: United States, 1991–1992 and 2001–2002. *Drug and Alcohol Dependence*, 74: 223–234.
- Grant, B. F. and Pickering, R. P. (1996). Comorbidity between DSM-IV alcohol and drug use disorders. *Alcohol Health Research World*, 20: 67–72.
- Hayes, N., Bagley, K., Hewlett, N., et al. (2023). Lived experiences of the diagnostic assessment process for fetal alcohol spectrum disorder: A systematic review of qualitative evidence. *Alcoholism: Clinical and Experimental Research*, (47)7: 1209–1223.
- Heilig, M., MacKillop, J., Martinez, D., et al. (2021). Addiction as a brain disease revised: Why it still matters and the need for consilience. *Neuropsychopharmacology*, 46: 1715–1723.
- Koob, G. F. (1992). Drugs of abuse: Anatomy, pharmacology and function of reward pathways. *Trends in Pharmacological Science*, 13: 177–193.
- Kranzlet, H. and Hartwell, E. (2023). Medications for treating alcohol use disorder: A narrative review. *Alcoholism: Clinical and Experimental Research*, 47(7): 1224–1237.
- Kraus, J., Morgenstern, H., Fife, D., Conroy, C. and Nourjah, P. (1989). Blood alcohol tests, prevalence of involvement and outcomes following brain injury. *American Journal of Public Health*, 79(3): 294–299.
- Lamb, R. J. and Ginsburg, B. C. (2018). Addiction as a BAD, a behavioral allocation disorder. *Pharmacology, biochemistry and behavior*, DOI:10.1016/j.pbb.2017.05.002. Epub 2017 May 2.
- Levy, N. (2013). Addiction is not a brain disease (and it matters). *Frontiers in Psychiatry*, 4. <https://doi.org/10.3389/fpsy.2013.00024>
- Lewis, D. C. (1991). Comparison of alcoholism and other medical diseases: An internist's view, *Psychiatry Annals*, 21: 256–265.
- Macdonald, V., Mathers, B., Sabin, K., et al. (2023). New data confirm lack of progress in harm reduction after three decades of proven evidence of effectiveness. *Addiction*, 118(8): 1411–1413.
- Robinson, T. E. and Berridge, K. C. (1993). The neural basis of drug craving: An incentive sensitization theory of addiction. *Brain Research Review*, 18: 246–291.
- Stone, B. (2022). Positive psychology for substance use disorders: A rationale and call to action. *Journal of Studies on Alcohol and Drugs*, 83(6): 959–961.

Biobehavioral Markers of Substance Use Disorders

17

Identifying the presence of or predicting risk for diseases or illnesses is an important part of prevention and intervention. Biomarkers have also been developed to identify risk for various diseases including psychiatric disorders, Alzheimer's, heart disease, genetic disorders and cancer. This complex and diverse field shares a common thread. Namely, the goal to identify markers for susceptibility, diagnoses, monitoring and predicting diseases or disorders. Technological advances in genetics and chemistry provide unprecedented tools to detect, identify, intervene or delay the medical consequences of SUDs as well. In this chapter, a broad approach to identifying SUD ranging from markers of acute use of a drug to markers predictive of medical consequences from long-term use that might benefit from intervention.

Identifying persons at risk can help clinicians prevent SUDs, seek treatment and develop prevention strategies and may include clinical screening questionnaires (e.g., CAGE, MAST AUDIT) as well as a number of biochemical indicators of abuse that can be found in commonly ordered hospital tests. Other tests that are not part of routine clinical chemistry testing may be available and are discussed below. Such tests provide the diagnostician and the patient with measurable and objective data that may be helpful in overcoming denial, predict medical problems and modifying outcome. The application of markers in studying SUDs can be behavioral, analytical or biological and not always with obvious applications. For example, simple analytical testing of wastewater can help develop community wide profiles of drug

use and consumption patterns or trends in drug use. These can be used to more precisely focus prevention resources within that community or region. Moreover, biomedical metrics such as heart rate, body temperature, blood pressure and pupil changes can be used as biomarkers to identify acute intoxication, whereas clinical biochemical markers such as liver enzymes, peptides, metabolites and proteins in blood can reflect tissue changes associated with chronic drug use. In this chapter, we will identify and review biobehavioral markers, toxicological, blood chemistry, neurochemical and genetic markers.

Basic Biobehavioral Markers

Although traditional biomarkers focus on predicting SUDs or their consequences and interventions, we begin our discussion of markers with basic and time-tested tools to identify human health and specifically acute intoxication. One of the oldest biomarkers of health is arterial pulse. Pulse was used to diagnose certain illnesses in ancient Chinese, Indian, Egyptian and Greek medicine. This was followed in the mid-19th century by blood pressure measurement, body temperature and then other biomarkers such as pupillary response. These basic biomarkers are a key part in the diagnosis of acute opioid intoxication (e.g., miosis, hypotension, bradycardia, hypothermia), stimulant intoxication (mydriasis, hypertension, tachycardia, hyperthermia), alcohol intoxication (horizontal gaze nystagmus, slow reaction to light and at high BACs, mydriasis, bradycardia, hypotension, vertical nystagmus). These basic and most commonly used biomarkers for acute drug intoxication are summarized in Table 17.1

These markers are often used by clinicians to make initial assessments of patients admitted to hospital for injuries. For example, rapid pulse (tachycardia) may be expected in an emergency room patient admitted for injuries and in pain or coupled with hypopnea, indicate a cardiac event. However, when tachycardia and gaze nystagmus are also present, it suggests intoxication (from alcohol or inhalants). Such markers are useful to confirm intoxication when it is suspected but may also indicate serious neurological or cardiac events requiring immediate medical treatment. These markers indicate acute effects of drug use but not predictive of future SUDs. In emergent situations, it is important to conduct a complete systems review, including prior history as medical complications following an injury or episode may present variable signs.

Table 17.1 Biobehavioral Markers for Acute Intoxication

Visual System	Horizontal Gaze Nystagmus ¹ (involuntary, rapid side to side, jerky movement of the eyes)	Alcohol, Inhalants
	Vertical Gaze Nystagmus ¹ (involuntary rapid up-down movement of the eyes)	Alcohol, Inhalants (high doses)
	Lack of Ocular Convergence ¹ (inability of both eyes to focus on nearby object)	Alcohol, Cannabinoids, Inhalants
	Slow pupillary reaction to light ²	Alcohol (high BAC), Stimulants, Opioids (little or no reaction)
	Miosis (pinpoint pupils: ≤ 3 mm in daylight) ²	Opioids
	Mydriasis (dilated pupils: ≥ 7 mm in daylight) ²	Alcohol (high BACs), Amphetamine, Cocaine, Hallucinogens, Cannabinoids
Cardiac	Bradycardia (low pulse: < 60 bpm) ²	Alcohol (high BACs) Opioids
	Tachycardia (increased pulse: > 100 bpm) ²	Amphetamines, Cocaine, Hallucinogens
Nervous System	Hyperthermia (increased temperature: $\geq 100^\circ$ F)	Amphetamines, Cocaine, Hallucinogens (stimulants in general)
	Hypothermia (decreased temperature: $\leq 95^\circ$ F)	Opioids
	Hypopnea (shallow breathing) ² Bradypnea (slow breathing) ²	Opioids (wooden chest syndrome)

¹Gaze nystagmus and decreased ocular convergence require specialized testing and except in extreme cases, not casually observed.

²Although consistent with intoxication (as indicated), when present, these signs may indicate a more serious, life-threatening condition requiring immediate medical intervention.

Toxicology

Toxicology results are another useful marker of specific drug use. They are objective and in a clinical setting, toxicology results may be useful in breaking through barriers of denial. In the workplace or in treatment, biomarkers of drug use can be used to monitor compliance. In legal matters, toxicology

results provide objective evidence of use and possible impairment, whereas in emergency medicine may indicate urgent treatment for an overdose or help identify the cause of cognitive or motor impairment (e.g., head injury vs. intoxication). There are two categories of toxicology tests: qualitative and quantitative.

Qualitative Drug Testing

In cases of acute intoxication, a urine toxicology screen can determine whether an individual had ingested a drug that is part of a “panel”. The most common panel is the NIDA 5, which includes urine testing for use of marijuana (THC), cocaine, amphetamines, opioids, and phencyclidine (PCP). Extended panels in the NIDA-10 includes testing for amphetamines, barbiturates, benzodiazepines, cannabis, cocaine, methadone, methaqualone, opioids, phencyclidine and propoxyphene. The NIDA panels do not include alcohol nor do affirmative results indicate intoxication. Such tests are usually reported as “positive” (one of the drugs was detected) or “negative” (no drug in the panel was detected). Most drugs are detectable in urine within 24 hours of use and remain detectable for much longer (see Table 17.2). Qualitative testing can help determine abstinence at the workplace, condition of parole or during treatment and provide a broad estimate of recent drug use. For example, if amphetamine is detected in urine, it can be concluded that the subject ingested amphetamine within about 1–2 days of when the sample was obtained because that is how long the amphetamine typically can be detected in urine. However, based only on a urine screen, the drug use could have been ingested hours or about days earlier. In some instances, such as workplace-required abstinence, a positive urine test may trigger more sophisticated analytical testing that is reviewed by a company Medical Review Officer who has special training in interpreting the results. There are qualitative tests available to detect drugs in hair and saliva.

Quantitative Drug Testing

Quantitative drug tests identify the concentration of the drug in blood or other tissues as well as body fluids. Depending on the route of administration, most drugs can be detected in blood within minutes of use and remain in blood for extended periods (see Table 17.2). Toxicology findings from a blood

Table 17.2 Detection Windows for Common Drugs of Abuse*

Drug	Urine	Blood	Saliva
Amphetamines	24 to 48 hours	12 hours	30 minutes to 36 hours (varies with lab test)
Barbiturates	2 to 15 days	1 to 2 days	
Benzodiazepines	3 days (short-acting) 30 days (long-acting)	2 to 3 days	
Cannabinoids (THC)	Several days (THC) to more than 30 days	1 to 2 days (THC)	
Metabolite (THC-COOH)	(THC-COOH), depending on frequency of use	2 to 14 days (THC-COOH)	
Cocaine or metabolites	2 to 4 days or more	1 to 2 days	
Opioids (general)	1 to 3 days	12 hours	
Methadone	2 to 14 days	2 to 3 days	
Morphine	24 to 72 hours	6 to 8 hours	
Phencyclidine	Up to 8 days	4 to 5 days 24 to 72 hours	

*Windows for drug detection vary with sample matrix, laboratory methodology, drug interactions and individual biological factors. Detection times are estimates.

sample are far superior biomarkers than urine tests and indicate the state of intoxication at the time the sample was obtained. Quantitative blood tests also allow estimates of how much of a drug was ingested and the results can be used to estimate the state of intoxication prior to the blood sample. This can be accomplished through the method of extrapolation. Extrapolation and pharmacokinetic analyses are widely used mathematical tools in medicine, pharmacology and other sciences to estimate projected results from a known value (e.g., blood test or other evidence). Such analyses are routinely used in the design of human research but require knowledge of the subject's physical characteristics (e.g., body weight, gender) and reasonable assumptions or known scientific factors, such as distribution of the drug in body water and the rate of elimination. This method is discussed elsewhere (Chapters 10, 18). As a biomarker, such results may speak volumes as to the ability of the subject to consume or administer large amounts of a drug characteristic of a drug use disorder.

Hair testing is another detection method. It has the ability to detect drug use far back in time but is not universally accepted and sample preparation is critical. Several studies have found that cocaine as well as cocaine metabolites can be detected in hair, even though the subject did not consume the drug. Although this is a convenient and non-obtrusive method, analytical testing should include both cocaine and cocaine metabolites (e.g., benzoylecgonine). Some studies have suggested that if the ratio of benzoylecgonine (BZE) to cocaine (COC) is less than 0.05, it suggests external COC contamination (e.g., from shampoos, sweat or surface contact or other sources). These testing ratios are still being researched, but currently, positive test of cocaine alone from hair samples should be cautiously interpreted.

Blood Chemistry Biomarkers

The search for new biomarkers for SUDs is ongoing. In considering new markers, five criteria should be considered. First, is the biomarker stable and persistent. This is important because substance use is often intermittent so the marker must be able to detect prior use even if the subject is tested during a period of abstinence. Second, the biomarker must be specific to differentiate co-morbid patterns of drug use, including legal drugs such as nicotine or byproducts of tobacco use. Third, the biomarker should be sensitive to cumulative drug use. Occasional use of most drugs does not have serious medical consequences but cumulative use over time does. Fourth, ideally the biomarker should be able to detect periods of use and abstinence such as before and after the start of treatment and fifth, a biomarker should be able to detect windows of exposure, such as prenatal exposure to a drug.

State vs. Trait Markers

There are two broad categories of biomarkers: state markers and trait markers. State markers flag recent drinking activity whereas trait markers potentially identify genetic predisposition to SUDs. Historically, alcohol use and disorders have dominated prevention research and as a result, more is known about biomarkers of alcohol intake than other SUDs. By examining enzymes present in blood, much can be learned about a person's alcohol use. The most common state markers are described below.

Gamma-Glutamyltransferase (GGT) is a large glycoprotein molecule made up of both proteins and carbohydrates found in liver cells (hepatocytes) and other cells, and is involved in digestion. Elevated GGT levels are an early indicator of liver disease and chronic heavy drinkers often have increased GGT levels. It takes up to 2 weeks of consumption of at least five drinks per day to elevate GGT and about 2 to 6 weeks of abstinence for blood concentrations to return to normal. However, GGT specificity and sensitivity vary respectively, from about 20 to more than 90 percent in identifying excessive drinkers in the general population. This biomarker can also be elevated by drugs other than alcohol or digestive diseases such as pancreatitis and prostate disease. Thus, the other physiological causes need to be considered before using GGT as a definitive marker of chronic heavy alcohol use.

Aspartate Aminotransferase (AST, formerly called SGOT) and Alanine Aminotransferase (ALT) are enzymes that help metabolize amino acids, the building blocks of proteins. Both AST and ALT concentrations are elevated in otherwise healthy people who drink at least three drinks or more per day for about a week and remain elevated for about 2 to 4 weeks. Of the two enzymes, ALT is the more specific measure of alcohol-induced liver injury because it is found predominantly in the liver, whereas AST is found in the liver, heart, muscle, kidney, and brain. Elevated AST and ALT are an indication of liver disease, associated with alcohol abuse but not necessarily a measure of alcoholism. But very high levels of these enzymes in blood (e.g., 500 units per liter) may indicate alcoholic liver disease. Clinicians often use a patient's ratio of AST to ALT (more than 2) to confirm an impression of liver disease due to chronic heavy alcohol consumption. These markers are most accurate in patients between the ages of 30 and 70.

Mean Corpuscular Volume (MCV), is a measure of the volume of red blood cells. Elevated MCV is associated with heavy chronic drinking of about 5 or more drinks per day over a period of 4 to 6 months. MCV remains elevated for about 2 to 4 weeks after abstinence. It may require several weeks or more of heavy drinking to elevate. Therefore, a detailed drinking history relative to a crime or accident in forensic investigations is necessary to infer anything about the more recent drinking history. In non-alcoholics the normal range for MCV is about 80–100 fL (femtoliters/cell) but varies slightly between laboratories and sample population. The use of MCV is specific to alcohol in more than 80 percent of patients. Values greater than 100 fL reflect macrocytotic

anemia and can also be due to other causes such as folic acid and Vitamin B12 deficiencies, both of which are common among alcoholics because of poor nutrition.

Carbohydrate-Deficient Transferrin (CDT) is a version of the glycoprotein transferrin, a molecule responsible for carrying iron within the bloodstream. Elevated CDT is very specific to alcohol use of about five or more drinks per day for 1 to 2 weeks. Drinking disrupts sialic acid's ability to attach to transferrin as well as other molecules. Many versions of transferrin normally are found in healthy people, but studies indicate that heavy drinkers have higher amounts of the CDT version than nondrinkers. Although it appears to be a highly specific measure of alcohol consumption with a low incidence of false positives, it also has a relatively high rate of false negatives and is difficult to analytically differentiate from other forms of transferring. In addition, even alcohol abstainers have low concentrations of CDT in their blood, and people with generally high concentrations of total transferrin will not necessarily have high absolute numbers of CDT molecules, regardless of their drinking status. Some patients who drink heavily do not show elevated levels of CDT. Researchers also find that, in general, women tend to have higher CDT levels than men, regardless of their drinking history. Despite the disadvantages of the CDT marker, it remains a very well-characterized biomarker for heavy alcohol intake and is associated with liver disease and anemia.

Phosphatidylethanol (PEth) is a phospholipid formed when alcohol is present. Since PEth is only formed if the subject has been drinking, it is a good marker. Although PEth has not been found to always track alcohol use subjects with mild AUD, the specificity of PEth for detecting drinking appears to be significantly higher (about 99 percent) as compared other popular markers. Several studies have concluded that PEth is both sensitive and specific to alcohol and increases in PEth are highly correlated with use, particularly hazardous drinking.

Other Biomarkers of Alcohol Use

N-Acetyl- β -Hexosaminidase (Beta-Hex), an enzyme found to be elevated in heavy drinkers, has been shown in some early studies to be both a sensitive and specific measure of heavy drinking. In addition, unlike MCV,

the increased beta-Hex returns to normal levels after only 7 to 14 days of abstinence. However, the beta-Hex assay is difficult to obtain in the United States, so clinicians have limited experience using it with different treatment populations. Other conditions, such as diabetes, pregnancy and hypertension, also appear to elevate beta-Hex. Most routine hospital lab tests would not include this enzyme.

Total Serum Sialic Acid (TSA). Because of sialic acid's clear potential as a highly specific marker for alcohol use, researchers have begun to study the potential of measuring total sialic acid (TSA) levels in patients' blood, rather than looking at the difference in sialic acid chains only on glycoproteins such as transferrin and apolipoprotein. Earlier studies demonstrate that, compared with social drinkers of both genders, both male and female alcoholics had elevated amounts of TSA. The test for TSA has similar sensitivity and specificity to the test for CDT for measuring alcohol consumption. However, because TSA levels take longer than either CDT or GGT to decrease during periods of abstinence, the TSA test might not be as useful for treatment programs assessing patients for relapse.

Acetaldehyde. As reviewed in Chapter 10, the metabolism of alcohol occurs via alcohol dehydrogenase, which results in the formation of acetaldehyde. Acetaldehyde can bind to proteins in blood such as oxygen-carrying hemoglobin for up to about 3 weeks after drinking. A large dose of about ten standard drinks will increase blood bound acetaldehyde, making it much more sensitive to occasional binge drinking episodes. Measuring whole blood-associated acetaldehyde is a very sensitive measure of alcohol use that can be used to monitor abstinence during treatment as well and is sensitive and precise enough to detect alcohol use for about a month after last use. Researchers are able to measure concentrations of both free and bound acetaldehyde in blood samples using high-performance liquid chromatography and fluorescence detection – known as the whole blood-associated acetaldehyde assay (WBAA). This assay is highly specific, extremely sensitive and has excellent precision. The insurance testing industry has used WBAA for more than a decade to test for heavy alcohol consumption (FDA approval for wider clinical use is currently pending). Its potential is even greater as a clinical tool to monitor people in alcoholism treatment programs, because this test can provide a picture of alcohol use over time. This works because, as a person continues to drink, hemoglobin-bound acetaldehyde accumulates in red blood cells over their life span (about 120 days) and this buildup shows

up as an increasing WBAA assay number. Levels of protein-bound acetaldehyde remain high for approximately a month after alcohol consumption (Halvorson, et al., 1993). The ability of the WBAA assay to measure alcohol consumption patterns over time makes it unique among the biomarkers described here.

Plasma 5-Hydroxytryptophol (5-HTOL). As discussed in Chapter 10, the metabolism of alcohol results in the formation of acetaldehyde. Acetaldehyde causes an increase in the production of hydroxytryptophol (5-HTOL), a metabolite of serotonin. Elevated 5-HTOL can be detected for about 24 hours and therefore provides evidence of heavy alcohol use within that period. The ratio of 5-HTOL with 5-hydroxyindoleacetic acid (5-HIAA), another metabolite of serotonin can be used to determine alcohol use. A urinary ratio of 5-HTOL:5-HIAA of more than 15 indicates that alcohol has been metabolized and therefore establishes alcohol use, even if alcohol is no longer in the blood. This biomarker is useful in determining compliance with abstinence in a treatment program and may have forensic value in determining if a subject consumed alcohol prior to death. One caveat to the use of this biomarker is that disulfiram (sometimes used as part of an alcohol abstinence program) may also increase 5-HTOL.

Fatty Acid Ethyl Esters (FAEE). The metabolism of alcohol produces acetaldehyde as well as fatty acid ethyl esters (FAEE). The detection of FAEE is from a combination of different molecules found in the liver, adipose, pancreas and hair. There are clinically insignificant effects of cosmetics and hair treatments on FAEE. Even so, FAEE concentrations vary along the length of the hair shaft, allowing some estimate of periods of abstinence or heavy drinking. The use of FAEE as a biomarker after death is potentially useful in establishing alcohol use.

Ethyl Glucuronide (EtG). Glucuronic acid is a compound that detoxifies drugs allowing them to be eliminated from the body through the urine. A minor route of alcohol metabolism occurs when alcohol reacts with glucuronic acid, producing a water-soluble ethyl glucuronide (EtG) that is easily excreted. The amount of EtG produced during alcohol metabolism is relatively low but can be detected in urine up to 5 days in urine and up to about 36 hours in blood. Even if no alcohol is present in the blood, the presence of EtG in body fluids indicates the person has consumed alcohol within that period. However, measuring EtG requires sophisticated equipment. In cases where

drinking alcohol poses a significant hazard, such as operating machinery, driving or flying planes or other situations where abstinence compliance is important, the lab must be specifically notified to check for EtG, since it is not part of a typical toxicology screen. Some studies indicate EtG can be detected in hair but is susceptible to use of cosmetics.

Salsolinol. This compound is formed in the brain when dopamine reacts either with acetaldehyde or pyruvate, a metabolite of glucose. Salsolinol is a potential neurotoxin associated with alcohol abuse. The usefulness of salsolinol varies based on the sample tested (e.g., urine or blood) and alcohol use history (alcoholics or non-alcoholics). Salsolinol is also found in various foods making changes in salsolinol as a direct result of drinking, difficult to confirm and differs depending on how it is measured. Salsolinol levels in urine have been found to decrease following acute alcohol consumption and measuring salsolinol levels in the blood may provide a better indication of chronic alcohol consumption.

Proteomics

Advances in the analysis of proteins (proteomics) now allow the detection of thousands of proteins in a single sample. Using proteomic testing, studies involving primates correctly identified heavy drinking with 100 percent sensitivity and differentiate abstinence from any amount of alcohol use with 88 percent accuracy in human studies. Matching proteins with certain genes to identify biomarkers of alcohol use in humans can identify subjects who consume more than ten drinks a day for at least 10 years. Patients with low levels of two specific protein markers, a fragment of fibrinogen αE and a fragment of apoprotein A-II, are low in alcoholics entering treatment (indicating long term excessive drinking) but increase about a week after entering treatment. Both protein fragments have potential as markers of excessive alcohol consumption in heavy drinkers seeking treatment.

Epigenetics

Genetics is the study of genes that regulate cell functions. DNA, which contains the genetic blueprint for life and is inherited and not changed by behavior or

the environment. Epigenetics is the study of how behavior and environment can change the way genes work and therefore behavior. Epigenetic changes regulate genes without permanently altering DNA. Epigenetic biomarkers of inherited traits such as addiction can be potential markers for SUDs since changes such in RNA and protein production may alter cell function that ultimately leads to changes in behavior. One such behavior of interest is drug-seeking and the reinforcing effect of a drug. Among the many potential epigenetic markers for SUDs, a small but specific segment of DNA is a promising biomarker for drug-induced changes that may signal risk.

The basic DNA sequence is not changed, proteins that might turn on or off certain cell functions do change with age, environment, diet and in response to drug exposure. One such epigenetic change involves a direct modification of DNA called DNA methylation. This change involves the transfer of a methyl group (CH₃) to the cytosine segment of the cytosine-phosphate-guanine (CpG) residue in the DNA. SUDs are brain based but it is not possible to take brain samples from subjects or patients for obvious reasons. However, there is evidence that changes in CpG methylation in peripheral sites such as white blood cells (leukocytes) and saliva correspond to changes in brain cells.

Epigenetic markers for tobacco smoking, alcohol, cannabis and opioid use have been identified. Of these, biomarkers for tobacco use shows considerable promise, but the literature for alcohol and other drugs is more limited.

Other Potential Biomarkers Requiring More Research

Since SUDs are ultimately a brain disease, researchers have focused on neurochemicals as possible trait markers. No clear front-runner in this line of investigation has appeared but are listed below as trait markers. Much more work is needed in this area.

Trait Markers

Trait markers are biochemical or genetic characteristics that may predict the manifestation of a SUD. Most research on trait markers has focused on alcohol use disorder. The following are the most widely examined markers.

Adenylyl Cyclase (AC) Activity

Found inside cell membranes, this enzyme provides cells with energy and while abundant in the body, the activity of AC in the blood platelet cells of abstinent alcoholics is lower than in nonalcoholics but increases when alcoholics resume drinking. Unfortunately, other drugs such as cannabinoids also affect AC activity. Further work is needed in order to use this as a more precise marker for alcohol use disorders alone.

Gamma-Aminobutyric Acid (GABA)

Differences in GABA levels are inherited and patients with alcohol dependence have lower levels of GABA than non-alcohol dependent patients. Since GABA is known to affect the effects of acute alcohol and benzodiazepines, this marker may reflect sensitivity to stress and alcohol use.

Dopamine

Dopamine is involved in the reward pathways in the brain. The greater the amount of dopamine activity, the more reinforcing whatever it was that increased dopamine activity. Male alcoholics who were abstinent for 7 years have lower dopamine receptor activity as compared with nonalcoholics but an increase in receptor activity within a week of withdrawal. Contradictory findings in other studies suggest the relationship between brain dopamine activity and alcoholism is more complex or that dopamine is not a good biomarker.

Beta-Endorphin

In Chapter 11 we learned that beta-endorphins are opioids produced by the pituitary gland that activate opiate receptors to reduce pain and cause various degrees of euphoria. Alcoholics and children of alcoholics have been found to have lower levels of beta-endorphin than non-alcoholics or their children. These findings indicate that differences in beta-endorphin levels are both specific to alcoholism and inherited.

Serotonin

Serotonin or other biochemicals associated with serotonin are potential markers for alcoholism. Tryptophan, an amino acid precursor for the manufacture of serotonin may be lower in heavy drinkers. Serotonin transporter activity in blood cells is higher in alcoholics (and their children) after abstinence suggesting this inherited marker for at-risk persons.

Drugs Other than Alcohol

The overwhelming majority of biomarker research focuses on alcohol. Although there is a large literature on the effects of other drugs on the brain, blood chemistry and biology. The literature on biological markers for other drugs is sparse. Epigenetic markers for cannabinoids and cocaine are promising but few studies have provided validated biomarkers for other drugs other than biobehavioral testing and toxicology to detect acute use. For now, toxicology screening and quantification remain the best biological markers of use for most other drugs.

Summary

Human behavior is complex as are patterns of alcohol or drug use. Detecting patterns of heavy drinking using biomarkers such as GGT, AST, ALT, CDT, MCV or proteomics remain popular in clinical use, identifying epigenetic biomarkers of quality and quantity or use will greatly improve in identifying and preventing SUDs by predicting behavior from the ocean of complex human experiences and genetics.

The search for ideal biomarkers of alcohol consumption and other drug use or for the predisposition toward a SUD is ongoing. Although the identification and use of markers to determine acute intoxication is well established, and many predictive markers of risk for SUDs exist or are under development, it is unlikely that one single marker will emerge. More likely, it will be a combination of biomarkers to identify drinking or drug use versus abstinence or confirming more subjective behavioral data suggesting drug use or SUDs.

Selected Bibliography

- Anderson, A., Dogan, M., Beach, S and Philibert, R (2015). Current and future prospects for epigenetic biomarkers of substance use disorders. *Genes*, 6: 991–1022.
- Anttila, P., Jarvi, K., Latvala, J. and Niemela, O. (2004). Method-dependent characteristics of carbohydrate-deficient transferrin measurements in the follow-up of alcoholics. *Alcohol and Alcoholism*, 39(1): 59–63.
- Arndt, T. (2000). Carbohydrate-deficient transferrin as a marker of chronic alcohol abuse: A critical review of preanalysis, analysis, and interpretation. *Clinical Chemistry*, 47(1): 13–27.
- Ballidin, J., Alling, C., Gottfries, C. G. et al. (1985). Changes in dopamine receptor sensitivity in humans after heavy alcohol intake. *Psychopharmacology*, 86: 142–146.
- Bean, P., Harasymiw, J., Peterson, C.M. and Javors, M. (2001). Innovative technologies for the diagnosis of alcohol abuse and monitoring abstinence. *Alcoholism: Clinical and Experimental Research*, 25(2): 309–316.
- Beck, O. and Helander, A. (2003). 5-hydroxytryptophol as a marker for recent alcohol intake. *Addiction*, 98(Suppl. 2): 63–72.
- Brick, J. (2006). Standardization of alcohol calculations in research. *Alcoholism: Clinical and Experimental Research*, 30(8): 1276–1287.
- Brick, J. (2008). Medical consequences of acute and chronic alcohol abuse. In: J. Brick (Ed.), *Handbook for the medical consequences of drug abuse*, 2nd Edition, The Hayworth Press, Taylor & Francis Group pp. 9–56.
- Carvalho Filho, R. J., Milani, A. N., Sampaio, J. P., Schiavon, L. L., Schiavon, J. N., Ferraz, M. L. G. and Silva, A. E. B. (2007). Distinguishing nonalcoholic fatty liver disease from alcoholic liver disease: Is ANI enough?. *Gastroenterology*, 132(5): 2076–2077.
- Cerovic, I., Mladenovic, D., Ješić, R., Naumovic, T., Brankovic, M., Vucevic, D., Aleksic, V. and Radosavljevic, T. (2013). Alcoholic liver disease /nonalcoholic fatty liver disease index: Distinguishing alcoholic from nonalcoholic fatty liver disease. *European Journal of Gastroenterology & Hepatology*, 25(8): 899–904.
- Chen, J., Conigrave, K. M., Macaskill, P. et al. on behalf of the World Health Organization and the International Society for Biomedical Research on Alcoholism Collaborative Group. (2003). Combining carbohydrate-deficient transferrin and gamma-glutamyltransferase to increase diagnostic accuracy for problem drinking. *Alcohol and Alcoholism*, 38(6): 574–582.
- Conigrave, K. M., Davies, P., Haber, P. and Whitfield, J. B. (2003). Traditional markers of excessive alcohol use. *Addiction*, 98(Suppl. 2): 31–43.
- Curtis, J. and Greenberg, M. (2008). Screening for drugs of abuse: Hair as an alternative matrix: A review for the medical toxicologist. *Clinical Toxicology*, 46: 22–34.
- Deitrich, R. A. and Erwin, V. G. (Eds), (1996). *Pharmacological effects of ethanol on the nervous system*. Boca Raton: CRC Press, pp. 51–72.
- Dunn, W., Angulo, P., Sanderson, S., Jamil, L. H., Stadheim, L., Rosen, C., Malinchoc, M., Kamath, P. S. and Shah, V. H. (2006). Utility of a new model to diagnose an alcohol basis for steatohepatitis. *Gastroenterology*, 131(4): 1057–1063.

- Freeman, W. M., Vanguilder, H. D., Guidone, E. et al. (2011). Plasma proteomic alterations in non-human primates and humans after chronic alcohol self-administration. *International Journal of Neuropsychopharmacology*, 14(7): 899–911.
- George, D. T., Rawlings, R. R., Eckardt, M. J. et al. (1999). Buspirone treatment of alcoholism: Age of onset, and cerebrospinal fluid 5-hydroxyindolacetic acid and homovanillic acid concentrations, but not medication treatment, predict return to drinking. *Alcoholism: Clinical and Experimental Research*, 23(2): 272–278.
- Haber, H., Jahn, H., Ehrenreich, H. and Melzig, M. F. (2002). Assay of salsolinol in peripheral blood mononuclear cells of alcoholics and healthy subjects by gas chromatography-mass spectrometry. *Addiction Biology*, 7(4): 403–407.
- Halvorson, M. R., Campbell, J. L., Sprague, G. et al. (1993). Comparative evaluation of the clinical utility of three markers of ethanol intake: The effect of gender. *Alcoholism: Clinical and Experimental Research*, 17(2): 225–229.
- Hatoum, A. and Colbert, S. (2023). Multivariate genome-wide association meta-analysis of over 1 million subjects identifies loci underlying multiple substance use disorders. *Nature Mental Health*, 1: 210–223. DOI:10.1038/s44220-023-00034-y
- Hock, B., Schwarz, M., Domke, I. et al. (2005). Validity of carbohydrate-deficient transferrin (%CDT), gamma-glutamyltransferase (gamma-GT) and mean corpuscular erythrocyte volume (MCV) as biomarkers for chronic alcohol abuse: A study in patients with alcohol dependence and liver disorders of non-alcoholic and alcoholic origin. *Addiction*, 100(10): 1477–1486.
- Hoffman, P. L., Glanz, J., Tabakoff, B.; and the WHO/ISBRA Study on State and Trait Markers of Alcohol Use and Dependence Investigators. (2002). Platelet adenyllyl cyclase activity as a state or trait marker in alcohol dependence: Results of the WHO/ISBRA study on state and trait markers of alcohol use and dependence. *Alcoholism: Clinical and Experimental Research*, 26(7): 1078–1087.
- Imbert-Bismut, F., Naveau, S., Morra, R. et al. (2009). The diagnostic value of combining carbohydrate-deficient transferrin, fibrosis, and steatosis biomarkers for the prediction of excessive alcohol consumption. *European Journal of Gastroenterology and Hepatology*, 21(1): 18–27.
- Jastrzębska, I., Zwolak, A., Szczyrek, M., Wawryniuk, A., Skrzydło-Radomańska, B. and Daniluk, J. (2016). Biomarkers of alcohol misuse: Recent advances and future prospects. *Przegląd Gastroenterologiczny*, 11(2): 78–89. DOI:10.5114/pg.2016.60252. Epub 2016 Jun 8. PMID: 27350834; PMCID: PMC4916243.
- Javors, M. A. and Johnson, B. A. (2003). Current status of carbohydrate-deficient transferrin, total serum sialic acid, sialic acid index of apolipoprotein J and serum beta-hexosaminidase as markers for alcohol consumption. *Addiction*, 98(Suppl. 2): 45–50.
- Johnson, R. D., Lewis, R. J., Canfield, D. V; and Blank, C. L. (2004). Accurate assignment of ethanol origin in postmortem urine: Liquid chromatographic–mass spectrometric determination of serotonin metabolites. *Journal of Chromatography B, Analytical Technologies in the Biomedical and Life Sciences*, 805(2): 223–234.
- Jones, A. W. (2023). Brief history of the alcohol biomarkers CDT, EtG, EtS, 5-HTOL and Peth. *Drug Testing and Analysis*, 2023: 1–18. DOI:10.1002/dta/3584.

- Mihic, S. J. and Harris, R. A. (2005). Alcohol actions at the GABA-A receptor/chloride channel complex. In: Mushhoff, F., Lachenmeier, D. W., Schmidt, P. et al. Systematic regional study of dopamine, norsalsolinol, and (R/S)-salsolinol levels in human brain areas of alcoholics. *Alcoholism: Clinical and Experimental Research*, 29(1): 46–52.
- Moore, L., Le, T and Fan, G. (2013). DNA methylation and its basic function. *Neuropsychopharmacology Reviews*, 38: 23–38.
- Mushhoff, F., Lachenmeier, D. W. and Schmidt, P. (2005). Systematic regional study of dopamine, norsalsolinol, and (R/S)-salsolinol levels in human brain areas of alcoholics. *Alcoholism: Clinical and Experimental Research*, 29(1): 46–52.
- Neumann, T. and Spies, C. (2003). Use of biomarkers for alcohol use disorders in clinical practice. *Addiction*, 98(Suppl. 2): 81–91.
- Nomura, F., Tomonaga, T., Sogawa, K. et al. (2004). Identification of novel and downregulated biomarkers for alcoholism by surface-enhanced laser desorption/ionization–mass spectrometry. *Proteomics*, 4(4): 1187–1194.
- Oroszi, G. and Goldman, D. (2004). Alcoholism: Genes and mechanisms. *Pharmacogenomics*, 5(8): 1037–1048.
- Oswald, L. M. and Wand, G. S. (2004). Opioids and alcoholism. *Physiological Behavior*, 81(2): 339–358.
- Peterson, C. M. and Polizzi, C. M. (1987). Improved method for acetaldehyde in plasma and hemoglobin-associated acetaldehyde: Results in teetotalers and alcoholics reporting for treatment. *Alcohol*, 4(6): 477–480.
- Petrakis, I. L., Trevisan, L., D’Souza, C. et al. (1999). CSF monoamine metabolite and beta endorphin levels in recently detoxified alcoholics and healthy controls: Prediction of alcohol cue-induced craving. *Alcoholism: Clinical and Experimental Research*, 23(8): 1336–1341.
- Ratsma, J. E., Van Der Stelt, O. and Gunning, W. B. (2002). Neurochemical markers of alcoholism vulnerability in humans. *Alcohol and Alcoholism*, 37(6): 522–533.
- Salem, R. O., Refaai, M. A., Cluett-Brown, J. E. et al. (2001). Fatty acid ethyl esters in liver and adipose tissues as postmortem markers for ethanol intake. *Clinical Chemistry*, 47(4): 722–725.
- Skrzydło-Radomańska, B. and Daniluk, J. (2016). Biomarkers of alcohol misuse: Recent advances and future prospects. *Gastroenterology Review*, 11(2): 78–89.
- Sorbi, D., Boynton, J. and Lindor, K. D. (1999). The ratio of aspartate aminotransferase to alanine aminotransferase: Potential value in differentiating nonalcoholic steatohepatitis from alcoholic liver disease. *The American Journal of Gastroenterology*, 94(4): 1018–1022.
- Stowell, L., Stowell, A., Garrett, N. and Robinson, G. (1997). Comparison of serum beta-hexosaminidase isoenzyme B activity with serum carbohydrate-deficient transferrin and other markers of alcohol abuse. *Alcohol and Alcoholism*, 32(6): 702–714.
- Swann, A. C., Johnson, B. A., Cloninger, C. R. and Chen, Y. R. (1999). Relationships of plasma tryptophan availability to course of illness and clinical features of alcoholism: A preliminary study. *Psychopharmacology*, 143(4): 380–384.

- Thompson, W. (2022). Alcoholism Workup. Medscape https://emedicine.medscape.com/article/285913-workup?reg_1&icd=login_success_email_norm#c6
- Torruellas, C., French, S. W. and Medici, V. (2014). Diagnosis of alcoholic liver disease. *World Journal of Gastroenterology: WJG*, 20(33): 11684.
- Toshikuni, N., Tsutsumi, M. and Arisawa, T. (2014). Clinical differences between alcoholic liver disease and nonalcoholic fatty liver disease. *World Journal of Gastroenterology: WJG*, 20(26): 8393.
- Volkow, N., Koob, G and Baler, R. (2015). Biomarkers in substance use disorders. *ACS Chemical Neuroscience*, 6(4): 522–525.
- Volpicelli, J., O'Brien, C., Alterman, A. and Hayshida, M. (1990). Naltrexone in the treatment of alcohol dependence: Initial observations. In: Reid, L. D. (Ed.), *Opioids, bulimia, and alcohol abuse and alcoholism*. New York: Springer-Verlag, pp. 195–214.
- Wang, J., Li, P., Jiang, Z., Yang, Q., Mi, Y., Liu, Y., Shi, R., Zhou, Y., Wang, J., Lu, W. and Li, S. (2016). Diagnostic value of alcoholic liver disease (ALD)/nonalcoholic fatty liver disease (NAFLD) index combined with γ -glutamyl transferase in differentiating ALD and NAFLD. *The Korean Journal of Internal Medicine*, 31(3): 479.
- Weng, J. T-Y., Wu, L. S-H., Lee, C-S., Hsu, P. W-C. and Cheng, A. T. (2015). Comparative epigenetic profiling analysis identifies DNA methylation changes associated with chronic alcohol consumption. *Computers in Biology and Medicine*, 64(3): 299–306.
- Wu, T. C., Tashkin, O. P., Djahed, B. and Rose, J. E. (1988). Pulmonary hazards of smoking marijuana as compared with tobacco. *New England Journal of Medicine*, 318: 347–351.
- Wurst, F. M., Alexson, S., Wolfersdorf, M. et al. (2004). Concentration of fatty acid ethyl esters in hair of alcoholics: Comparison to other biological state markers and self-reported ethanol intake. *Alcohol and Alcoholism*, 39(1): 33–38.
- Wurst, F. M., Skipper, G. E. and Weinmann, W. (2003). Ethyl glucuronide—The direct ethanol metabolite on the threshold from science to routine use. *Addiction*, 98(Suppl. 2): 51–61.
- Yegles, M., Labarthe, A., Auwarter, V. et al. (2004). Comparison of ethyl glucuronide and fatty acid ethyl ester concentrations in hair of alcoholics, social drinkers and teetotalers. *Forensic Science International*, 145(2/3): 167–173.
- Yoneda, M. (2007). Usefulness of a new model to diagnose alcoholic liver disease in patients with steatohepatitis. *Nature Clinical Practice Gastroenterology & Hepatology*, 4(5): 258–259.
- Zalewska-Kaszubska, J. and Czarnecka, E. (2005). Deficit in beta-endorphin peptide and tendency to alcohol abuse. *Peptides*, 26(4): 701–705.

Forensic Issues in Psychopharmacology

18

The effects of drugs in crimes and accidents are of central forensic value. Some drugs, such as alcohol, have a well-established deleterious effect on driving, for example. Marijuana use also impairs driving but its effects are limited and other intoxicating drugs do not clearly contribute to impaired driving even though they are associated with behaviors that could affect motor vehicle operation. While there is no doubt that alcohol and many other drugs impair multiple domains of human behavior, the mere presence of a drug does not mean that intoxication was the cause of an event. In this chapter, we discuss the scope of the problem, detection and measurement of alcohol and drugs and critical questions in interpreting drug test findings. Applied pharmacology and other factors need to be considered in reconstructing the role of alcohol and other drugs on behavior, particularly when there is a question of forensic interest.

Forensic Considerations

The increase in available medical statistics on the effects of alcohol and other recreational drug use, and even from therapeutic drug use, has led to a greater interest in the role of psychoactive drugs in crimes and accidents investigated by law enforcement, public health officials and others. Similarly, expansion of the enforcement of drunk driving laws to include other drugs, along with popular television shows, have heightened public awareness and interest about forensics. Forensic science (forensics) is the application of a particular field of science to a question of law. Forensics includes many different scientific

applications, including but not limited to: DNA matching, fingerprinting, voice analysis, ballistics, psychology, accident reconstruction, dentistry, nursing, medicine, entomology (and other aspects of wildlife biology) and psychopharmacology. Because this topic interests so many people, topics of forensic interest for various drugs, including alcohol can be found in each chapter of *Drugs, The Brain and Behavior*. In this chapter, we review some of the practical methods of applying principles in pharmacology to issues of forensic interest. For example, was the dose or concentration of a drug high enough to cause death or impair driving?

Scope of the Problem

Drug use, misuse and overuse (including medications, street drugs, alcohol) are relatively widespread throughout most of the world including the United States, where most high school age children have experimented with many drugs including alcohol. All too often drug and alcohol use results in criminal or fatal consequences. How common is drug or alcohol use? In the US about 78 percent of people age 12 or older have consumed alcohol at some time in their life. Among older (18+) persons, about 45 percent have consumed alcohol at some point. A better indicator of who drinks regularly comes from surveys about alcohol use in the last 30 days. About 50 percent of men (age 12 and older) and 45 percent of women (age 12 and older) have consumed alcohol in the last month. Among adults about 52 percent have consumed alcohol in the last month. Generally, men report alcohol use slightly more than women.

Self-report data show that about 10 percent of high-school seniors have driven a car after heavy drinking (defined as five or more drinks in a row) and 12 percent have been passengers of such drivers. About 13 percent and 23 percent of high-school students smoked marijuana or were passengers of a driver who smoked, respectively. In the US, by the time children graduate from high school, nearly half (48 percent) have used an illicit drug. Worldwide, the four most commonly used addictive substances are cocaine (highest world-wide use in North America and Oceania), cannabis (highest world-wide use in North America, Oceania, West Central Africa and Western Europe), tobacco (highest world-wide use in islands in Micronesia and subregions of Oceania and south Pacific islands; France, Germany, Poland and the United States). Alcohol use is extremely high world-wide with life-time use greater than 90 percent in the Americas and Eastern Europe.

Detection and Measurement of Drugs

There are five common sample types (or matrixes) in which drugs, including alcohol, are routinely detected in the human body: (1) breath testing (in the case of alcohol); (2) serum testing, which is used primarily in hospitals (alcohol and other drugs); (3) blood testing (alcohol and other drugs); and (4) urine tests (drugs, medications, and alcohol) and; (5) other tissues such as heart, brain or fluid from the eye (vitreous). Biobehavioral indicators used by specially trained law enforcement agents (DREs) rely upon basic physiological changes (e.g., pupil size and response, nystagmus, blood pressure) that may assist during an investigation. While the measures are generally associated with certain classes of drugs, they are not quantitative, do not always differentiate between intoxication and medical conditions and not included in this discussion. New methods based on voice spectrographic signatures show potential in indentifying intoxicated persons. This interesting method is evolving and holds promise when an in-person intervention is not available but it has not attained acceptance as forensic evidence.

Breath alcohol testing is based on the principle that once equilibrated in blood, alcohol that passes through the alveoli of the lungs is proportional to the concentration in blood based on a partition coefficient ratio. This ratio reflects the concentration of alcohol in blood to the small amount of alcohol in expired breath. Breath and blood alcohol are very highly correlated and breath testing is a reliable method (assuming proper technician training and accurate standardization) to detect alcohol in blood.

Serum alcohol testing is often performed in hospitals. Blood is separated into cells and serum (the watery portion of the blood). Since alcohol is distributed throughout the watery portions of the body, including the blood, the serum sample contains more water than the whole blood from which it is derived and the concentration of alcohol in whole blood is less than that of the serum in proportion to their respective water contents. Under normal physiological conditions, a serum alcohol value can be converted to its whole blood equivalent by multiplying it by .85, or dividing it by the reciprocal, which is 1.18. If the hematocrit value (the percentage of red blood cells in a fixed volume of blood) is available from a hospital record the whole blood alcohol equivalent from serum can be calculated more precisely. The method to convert serum alcohol to whole blood alcohol accounts for gender and actual differences in the water content of the blood is as follows:

Serum to blood alcohol conversion for men =
 $(\text{Hct} \times 0.645) + ((100 - \text{Hct}) \times 0.95) / 95$

Serum to blood alcohol conversion in women =
 $(\text{Hct} \times 0.608) + ((100 - \text{Hct}) \times 0.95) / 95$

Blood, serum, or urine alcohol or drug tests employ different analytical methods. In most crime laboratories, alcohol and other drugs are detected using a highly specific method called gas chromatography (GC) or GC coupled with mass spectroscopy (GC-MS) to detect minute quantities of drugs. These methods are very specific and represent the gold standard in analytical chemistry.

Blood testing is a direct measure of the concentration of a drug in circulation to the brain. Information about the biobehavioral and other effects of drugs is available primarily through blood (or breath) testing. Relating behavior to drug concentrations in the brain or other organs cannot be easily obtained without serious injury to the subject! However, there are new technologies (e.g., Proton Magnetic Resonance Spectroscopy) that allow the measurement of low concentrations of drugs in the brain in living subjects while performing limited cognitive tasks.

Urine testing is an easier, faster, and more economical way to screen for metabolites or breakdown products of a drug in urine. However, such tests only indicate use of the drug at some time based on the half-life of the drug and what is detected (e.g., parent compound or a metabolite). Urine toxicology tests are sometimes quantitative but even so, do not reveal if the subject is under the influence of the drug at the time of testing. A positive urine test often leads to a confirmational test (GC-MS) to specifically identify the drug based on its unique molecular signature. Also, most hospital and some forensic labs detect drugs in urine only. Such tests rarely provide information about the effect of the drug on behavior since the urine is never in contact with the brain. Urine testing can detect the presence of drug use for varying periods (see Table 17.2, Chapter 17).

Hair testing is a potentially effective but relatively new means of identifying illegal drug use using a radioimmunoassay (RIA). RIA is a very well established and accepted methodology and can detect the use of many drugs (amphetamine/methamphetamine, cocaine and cocaine metabolites, codeine, heroin metabolite, cannabis and phencyclidine) for up to 90 days. More specific follow-up testing using liquid chromatography/mass spectroscopy (LC/MS) should be employed in most cases. However, courts in the US

do not universally accept hair testing. Several studies have demonstrated that environmental cocaine exposure, shampoos or other factors such as environmental exposure can lead to false positive hair cocaine results. Also, like urine testing, hair testing only indicates use at some point (up to 3 months prior to sampling) and reveals nothing about intoxication or impairment. See Chapter 17 for additional discussion on hair testing limitations.

While psychoactive drugs are clearly represented in a variety of legal matters and accidents, the hazards posed by some drugs to users have been the subject of considerable debate within the scientific community. Epidemiology studies of drugs and car crashes and laboratory studies demonstrate multiple domains of impairment by drugs as a significant factor in motor vehicle (or other) injuries, but this is not a universal finding. For example, in urine tests, the mere presence of a drug or its metabolite cannot be used to conclude that the subject was under the influence of that drug. Blood tests that measure cocaine, methadone, and cannabis are often misinterpreted. For example, there is a body of scientific research showing that cocaine does not impair driving under most circumstances. Exceptions to this include very high cocaine doses or post-euphoric “crash”. Similarly, driving is not impaired in patients receiving long-term methadone treatment for opioid addiction but a recent increase in methadone dosing may produce impairment that is similar to other opioids. Finally, while cannabis impairs driving, the effects of this drug are limited to a few hours, even though THC or THC metabolites can be detected for many hours after use.

Interpreting Toxicology Findings

Knowledge of the therapeutic, recreational, or lethal dose (LD) of a drug can be useful in interpreting a laboratory test report or overdose, as well as understanding the pharmacokinetics of the drug. For example, heroin remains in the blood for only minutes before it is metabolized to another compound. If someone were suspected of using heroin, it would be virtually impossible to actually detect heroin. Without an understanding of the pharmacology of the drug, less experienced persons may erroneously conclude the drug was never used.

The interpretation of toxicological test evidence and the causal relationship between drug use and motor vehicle operation must be examined in the

context of the following critical questions: (1) Is there proof that the drug has been consumed? (2) Could the amount of the drug detected produce impairment? (3) Is there biobehavioral evidence of impairment specific to the drug in question? and (4) Could this amount of drug have contributed to some event (such as an injury)?

Applied Pharmacology

We previously reviewed (in Chapter 3) the basics of pharmacokinetics and that psychoactive drugs are distributed through the blood to the fatty and watery portions of the body. Differences in body size, gender, age, and height will affect the amount of total body water (TBW) available for a hydrophilic (water-seeking) drug to be distributed in the apparent volume of distribution (V_d). Knowledge of the subject's V_d , the half-life of the drug (or rate of elimination) allows pharmacological calculations to determine how much drug was ingested or, with additional information, about when the drug was ingested and the state of intoxication. For alcohol, these values are calculated based on different anthropometric values (age, weight, height and gender) whereas for other drugs, published data of the V_d for a particular drug often has a range reflecting the unspecified diversity of anthropometrics within the sample size studied.

How Long Before the Drug Concentration is Zero?

The time it takes for a drug concentration to reach zero, or at least below the detection threshold of sensitive analytical instruments, depends on the half-life of the drug. Table 3.1 shows that regardless of how high the drug concentration is, for all practical purposes, the drug will be out of the body or so low as to be undetectable in about seven half-lives. For example, heroin has a half-life of 2–6 minutes and would be undetectable in blood after 14–42 minutes. In a DUI (driving under the influence) or DWI (driving while intoxicated) case, this would probably be insufficient time between the arrest and blood testing to detect heroin. However, heroin is metabolized to morphine, which has a much longer half-life (about 1–7 hours), so it would be detectable in blood for about at least 7 hours. Some drugs have more than one half-life, depending on different factors including time and drug concentration, but generally, the

half life is a valuable concept that can answer the question: “how long will a drug be in my body?”.

How Much Drug Was Ingested?

In scientific research, medical treatment or forensic examination, there are many occasions when it is important to know how much drug was ingested or what the concentration of the drug would be, given a known dose. The following simplified examples illustrate how pharmacological principles can be applied to answer a question of forensic interest.

Clinical Case Study 1. Was Xanax Used According to Prescription or Was It Misused?

Consider a case in which a student has a prescription for 2 mg Xanax (an anti-anxiety medication) to be taken as needed. Blood testing revealed 0.02 mg/L of the anti-anxiety drug alprazolam (Xanax). Was the person taking the drug as prescribed, or abusing the drug by taking high doses? Alprazolam has a V_d of about 1 L/kg (range 0.9–1.3 L/kg). The V_d , along with other information, can tell us how much alprazolam was in the circulation at the time of the blood test. To calculate the circulating dose (D), use the following pharmacokinetic equation:

Equation 17.1.

$D = V_d \times \text{body weight (in kilograms)} \times \text{concentration of drug in plasma}$
If $D = V_d$ (1), body weight = 82 kg, and drug concentration is .02 mg/L, then:

$$D = (1 \text{ L/kg}) \times (82) \times (.02 \text{ mg/L}) = 1.64 \text{ mg}$$

This is the amount of alprazolam in blood at the time of testing. Since alprazolam has a relatively long half-life of 6–27 hours (average 11 hours) it is likely that the subject was taking alprazolam properly, since a dose of 1–2 mg of alprazolam is within the therapeutic window for this drug. Since it takes a long time for alprazolam to be metabolized, the amount detected probably reflects a therapeutic as needed use of the drug as prescribed.

Clinical Case Study 2. A woman (age 23, 110 pounds and 66 inches tall) is arrested for DWI, has a blood alcohol concentration (BAC) of 0.08 percent (80 mg/dL) and claims she only consumed one regular beer 2 hours earlier. Is this possible?

An initial calculation of the circulating alcohol burden (CAB) is made that is independent of other factors such as when drinking occurred or the subject's rate of alcohol elimination.

Using modern approaches scientists have more accurately estimated the Vd for alcohol using individual measures of body mass or total body water algorithms. Watson and colleagues derived algorithms for TBW based upon gender, age, weight, and height. Most current methods for estimating body water for alcohol are accurate, but in our experience, the Watson algorithm is the best method to use to determine drug distribution in body fluid. This method has been widely validated and applied by alcohol researchers. Using the following equations the Vd can be calculated as follows:

Equation 18.2: For men less than 16 years old:

$$-21.993 + (0.406 (\text{lb.}/2.2045)) + (0.209 (\text{ht}''/2.54))$$

Equation 18.3: For men 17 to 86 years old:

$$2.447 - (0.09516 \text{ age}) + (0.1074 (\text{ht}'' 2.54)) + (0.3362 (\text{lb.}/2.2045))$$

Equation 18.4: For women less than 16 years old:

$$-10.313 + (0.252 (\text{lb.}/2.2045)) + (0.154 (\text{ht}'' 2.54))$$

Equation 18.5: For women 17 to 84 years old:

$$-2.097 + (0.1069 (\text{ht}'' 2.54)) + (0.2466 (\text{lb.}/2.2045))$$

Using the appropriate algorithms, the total body water Σ_{vd} for the subject in our example would be about 28.13. Solve for CAB using Equation 18.6.

$$\text{Equation 18.6 } \text{CAB} = (\text{BAC}_{\text{obj}} \times \Sigma_{\text{vd}}) / 80.65$$

Where BAC_{obj} is the blood test result of .08 percent and 80.65 the water content of blood.

$$(80 \text{ mg/dL} \times 28.13) / 80.65 = 27.9 \text{ grams}$$

Since 28 grams is equal to 24 ounces of 5.0 percent (v/v) alcohol (i.e., typical American beer), and because alcohol elimination begins with the first drink (more than two hours earlier), it is a scientific certainty that the subject consumed more than two twelve-ounce 5.0 percent (v/v) beers.

Incorporating other factors, such as the time from the start of drinking to the last drink, a range of alcohol elimination rates and algebraically rearranging Equation 18.6 and accounting for absorption and elimination can answer other questions of forensic interest.

Clinical Case Study 3. A man consumes alcohol over a period of 6 hours, operates a motor vehicle and 1 hour later on the way home, loses control of his vehicle and crashes into another vehicle, killing the occupant. A blood test revealed a BAC of .08 percent 3 hours after the crash. How intoxicated was the driver at the time of the crash?

This question can be answered by applying principles in pharmacokinetics. In Chapters 3 and 10 we reviewed some simple calculations to estimate BAC. Often, forensic analyses require estimates of the BAC at various times prior to a blood sample or event (e.g., motor vehicle crash). Consideration of the body compartments and other factors can provide accurate estimates the BAC range over time. In criminal (and civil) cases, a prosecutor or district attorney may ask what the BAC was at the time of a motor vehicle crash. Too often, when chemists or toxicologists are asked to make such determinations, they do not appreciate the two most important physiological factors in such calculations: absorption and elimination and apply a constant to each. Alcohol absorption and rates of elimination vary and failure to consider this fact leads to inaccurate answers. The absorption rate varies from about .01 percent to .06 percent (typically .02 to .05 percent) of the total alcohol volume in the stomach distributed over the period. In practice, this corresponds to maximum BACs about 90 to 15 minutes, respectively, after the last drink, depending on the drinking circumstances. This can be expressed in calculus terms as $d(A_s)/dt$, where A_s is the absorption rate and dt is the time from the first drink to the blood.

Similarly, the rate of alcohol elimination varies from slower metabolizers to faster metabolizers, corresponding to elimination rates of about 10 to 25 mg/dL/hr. Rates outside these ranges are possible particularly in some clinical populations but rare and in forensic analyses require some objective basis,

not possibilities. In forensic cases, the legal standard is to a reasonable degree of scientific probability or certainty, not possibility.

When these variables are applied to pharmacokinetic calculations, the results provide accurate estimates of intoxication over time. In the hypothetical example, the actual analytical results show the driver had a BAC between .09 percent and .14 percent (Figure 18.1). Depending on other facts such as recent or not recent eating the range of results may be narrowed down. Otherwise, all that can be said is that the driver had a BAC as low as .09 percent and as high as .14 percent at the time of the crash. The conceptual methodology of this is described in Figure 18.1 and as explained above.

Clinical Case Study 4. Could You Die from a Caffeine Overdose?

What if you wanted to know if a dose of caffeine (from coffee) would be lethal? In the United States, a cup of coffee contains up to about 150 mg of caffeine. Calculating the predicted drug concentration is an algebraic rearrangement of the Equation 18.1 into the formula below.

Equation 18.7

$$C = A / Vd$$

where C = concentration (mg/L)

A = dose absorbed (mg/kg)

Vd for caffeine = 0.5 L/kg

If a 120-pound woman drank 40 cups of coffee (rapid absorption assumed), her estimated caffeine concentration is calculated from Equation 18.7 to be as follows:

$$A = (20 \times 150 \text{ mg}) = 6000 \text{ mg}$$

$$\text{kg} = (120 / 2.2054) = 54.4$$

$$Vd = 54.4 \text{ kg} \times 0.5 \text{ L/kg} = 27.2 \text{ L}$$

$$6000 \text{ mg} / 27.2 \text{ L} =$$

$$221 \text{ mg/L}$$

Caffeine concentrations of 179–344 mg/L (average 183 mg/L) have been reported to be fatal in multiple cases. Therefore, it would be dangerous and probably fatal to drink such a large amount of coffee.

JOHN EDWARD WALKER

Accident: 1:00 AM; Bac = 0.08% at 5:00 AM; $r(\text{abs})=30-90'$; $r(\text{elim})=0.01-0.02\%/h$; $V_d=46.5$

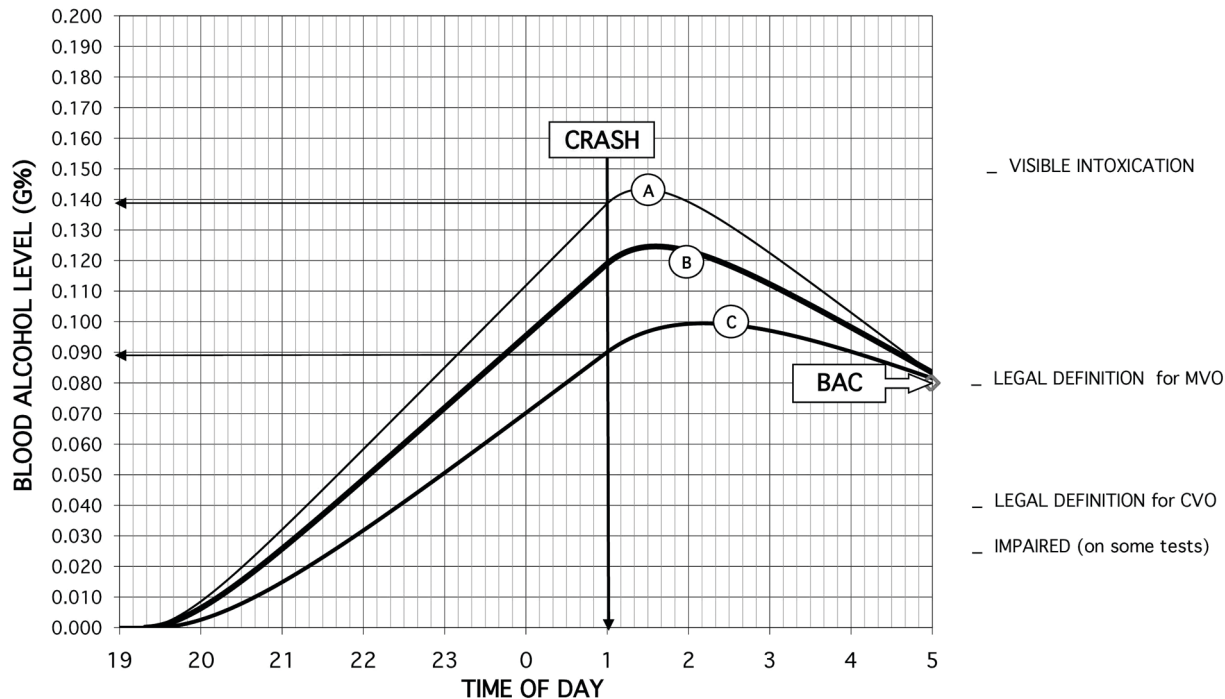


Figure 18.1 Flow chart of the scientific parameters in calculating the BAC over time

Drug Interactions

Drug interactions are an important topic in pharmacology and particularly in psychopharmacology. One of the largest literatures in psychopharmacology involves the effects of alcohol. Alcohol is a socially accepted legal drug that produces medical and psychosocial effects in every facet of society and the drug most commonly detected in toxicology reports, hospital admissions and accidents. Consequently, our discussion of drug interactions will focus on alcohol as a common denominator with drug interactions.

Why More than One Drug at a Time?

There are several reasons why people use more than one drug at a time. In most instances, the user's goal from multiple drug administration is to increase the primary drug effect. Many drug effects are increased when another drug is added, increasing the intensity of the "high". Other times, another drug may be taken to decrease the undesirable side effects of the primary drug. For example, long-term use of some antipsychotics results in a motor disorder (tardive dyskinesia) that is similar to Parkinson's disease. To minimize tardive dyskinesia, another medication such as Bzotropine (e.g., Cogentin) might be administered. Cogentin is also used to treat Parkinson's disease. Another example is the use of medical marijuana to offset the effects of cancer treatments. Similarly, alcohol or some other depressant may be used to alleviate the edgy feeling many people experience after the desired effects of a stimulant wear off. When the availability of the drug of choice is limited, another drug may be used because of the limited supply of the primary drug. Heroin addicts, for example, often drink large amounts of alcohol or use other depressants to reduce or delay the opioid withdrawal syndrome or until additional narcotics can be procured. Finally, sensation seeking may be the goal of some individuals without any regard to safety or rationale other than to become more intoxicated.

Pharmacological Basis of Alcohol-Drug Interactions

Drug interactions can produce alterations in physiology and ultimately behavior by changing drug pharmacokinetics or changing pharmacodynamics. Pharmacokinetic mechanisms account for drug interactions

when the presence of one drug affects the bioavailability of another drug. Pharmacodynamic interactions account for drug interactions when drugs interact at the receptor level.

Pharmacokinetic Interactions

Pharmacokinetic interactions alter the bioavailability of the drug. The greater the availability of the drug to increase or decrease the functional activity of neurotransmission, the greater the effect will be. Pharmacokinetic interactions can occur through changes in drug absorption, distribution, metabolism and excretion.

Absorption

Delays or acceleration in absorption can alter the amount of drug that enters the circulation (bioavailability). The most common site for such an interaction would be through the gastrointestinal system. For example, alcohol increases the absorption rate of some benzodiazepines, so that more drug will enter the circulation than if the drug were taken without alcohol in the stomach. Another example is the effect of the antibiotic erythromycin. Erythromycin increases the rate of gastric emptying so that any drugs that would be partially metabolized by stomach enzymes, such as gastric alcohol dehydrogenase are likely to reduce first-pass metabolism of alcohol in the stomach resulting in potentially higher BACs.

Distribution

Once a drug is absorbed from the gastrointestinal tract into the circulation it is distributed throughout the watery portions of the body. The total amount of body water available for a drug to enter will change the concentration of the drug. The greater the body water volume the lower the blood drug concentration and the smaller the water volume, the greater the concentration will be. If a drug changes the volume of distribution of another drug will alter the effectiveness of that drug. For example, alcohol increases the volume of distribution of cocaine, which may decrease the concentration of cocaine in the circulation when both drugs are present.

Metabolism

Drugs are subject to biotransformation at different sites in the body and via different physiological mechanisms. The process of metabolism is essential to life but also to understanding some drug interactions. For example, a particular family of enzymes, cytochrome P450 are located in almost every living thing – plants and animals, bacteria and even viruses. This family of super enzymes consists of many different isozymes and plays an important role in the metabolism of many drugs. The major isoenzymes involved in drug metabolism are CYP3A4, CYP2D6, CYP1A2, CYP2E1 and the subfamily of CYP2C. When two drugs are metabolized by the same enzyme the presence of one drug can alter the metabolism (and thus the bioavailability) of the other drug.

For example, ethyl alcohol and methyl alcohol compete for the same enzyme, alcohol dehydrogenase. Methanol is very toxic because it is metabolized to formic acid (see Chapter 10). Ethyl alcohol is preferentially metabolized over methanol so it prevents methanol from being transformed. A similar form of preferential metabolism can be found when a popular anticoagulant is co-administered with alcohol. Warfarin (Coumadin®) is prescribed as an anticoagulant and often prescribed to treat patients with artificial heart valves or following open-heart surgery. Warfarin is metabolized by the cytochrome P450 enzyme system in the liver. This is one of the systems involved in alcohol metabolism. Alcohol is preferentially metabolized over warfarin so drinking while taking warfarin will increase its anti-clotting effect potentially resulting in hemorrhages. However, in chronic drinkers, alcohol increases the cytochrome P450 system resulting in over metabolism of warfarin and a decrease in its ability to protect against dangerous blood clots.

Excretion

The removal of drugs from the body through the sweat in urine is based on the electrical charge of the drug. Changes in the acidity of the urine that might result from respiratory or metabolic acidosis or alkalosis can alter drug elimination. For example, drugs that are weak acids (such as salicylate and phenobarbital) are rapidly excreted when the urine is alkaline. On the other hand, renal excretion of alkaline drugs (such as amphetamines and phencyclidine) is enhanced when the urine is acidic. Shifts in the acid-base physiology may

therefore alter drug bioavailability. Very small amounts of some drugs can be excreted in sweat, as well.

Pharmacokinetic and pharmacodynamic interactions

Such interactions deserve consideration in forensic situations. For example, cimetidine is a medication to treat gastric ulcers. One of its actions is to inhibit gastric alcohol dehydrogenase, the same enzyme found in the liver that metabolizes alcohol. Use of cimetidine may increase the bioavailability of alcohol entering the circulation because it is not being metabolized in the stomach. This pharmacokinetic interaction may be important in a small percentage of legal cases. Pharmacodynamic interactions more typically apply to forensic cases.

For example, an *additive effect occurs* when a combination of two drugs is equal to the sum of the effect of each drug (e.g., $2 + 2 = 4$). For example, alcohol and benzodiazepines have reported additive effects. Fentanyl mixed with Xylazine (an animal tranquilizer) is a recent drug combination trend. Xylazine alone is dangerous and when combined with fentanyl the effects are at least additive and possibly synergistic.

Synergistic effect (also called “potentiation”): when the combination of two drugs produces an effect greater than the effect of both drugs (e.g., $2 + 2 = 6$). For example, both alcohol and carbon tetrachloride, a cleaning fluid, are toxic to the liver. However, their combination produces far greater liver damage than would be predicted from the sum of the effects of either substance.

Antagonistic: when one drug blocks the effect of another (e.g., $2 + 2 = 1$ or $2 + 2 = 0$). This term is often used to describe the specific actions of receptor antagonists or blockers. For example, naloxone is an opioid antagonist. It occupies opioid receptors to block the effects of drugs like heroin.

Toxicology Findings After Death

Post-mortem toxicology results need to be interpreted on a case-by-case basis. In cases resulting in death, blood and other tissue samples are often obtained at autopsy by the medical examiner and sent to a laboratory for analysis. The concentration of alcohol and other drugs in vitreous fluid, brain, or other tissue is quantitatively different from blood because of differences in water content and distribution. Measuring drug concentrations at different

anatomical sites may provide forensic clues as to how recently a drug was ingested, accuracy of overall testing, or other physiological conditions that may explain why a person died.

However, many drugs exhibit “post-mortem redistribution” (PMR) in which the concentration of the drug varies among selection sites. Tricyclic antidepressants and many other therapeutic and non-therapeutic drugs may be subject to PMR. Obtaining a blood sample from a central site near the heart may have significantly higher concentrations than blood taken from a peripheral site, such as a femoral blood vessel in the leg. Alcohol is not generally affected by PMR unless the victim died with a large amount of alcohol in their stomach or there was contamination from the gastrointestinal system. This potential problem is significantly eliminated if blood samples are obtained from a peripheral site, such as a femoral blood vessel. In any case, post-mortem toxicology results should be interpreted carefully in forensic matters.

Summary

Alcohol and drug use disorders often result or are noted in crimes or accidents that require interpretation of toxicology test results. The application of principles in pharmacology to answer a forensic question about the role of a drug in some event is often useful in discussing alcohol or drug use with a patient, the family or explaining such findings in a court of law. Different analytical tests have been developed to provide basic, static information about the concentration of alcohol or another drug at the time of testing. As an introduction to this topic, this chapter overview does not include all facts or scientific assumptions or answer questions related to specific individuals. Applied pharmacokinetics should be performed by an experienced scientist and include the totality of evidence, before it can be useful in answering forensic questions about psychoactive drug use and intoxication.

Selected Bibliography

- Brick, J. (2006). Standardization of alcohol calculations in research. *Alcoholism: Clinical and Experimental Research*, 30(8): 1276–1287.
- Brick, J. (2008). Medical consequences of acute and chronic alcohol abuse. In: J. Brick (Ed.), *Handbook for the medical consequences of drug abuse*, 2nd Edition, The Haworth Press, Taylor & Francis Group, pp. 9–56.

- Brick, J. (2013). Alcohol: Interaction with other drugs *Wiley encyclopedia of forensic science*, Jamieson, A. and Moenssens, A. (Eds), Chichester, UK: John Wiley & Sons, Ltd.
- Brick, J. (2016). *Forensic Alcohol Test Evidence (FATE): A handbook for law enforcement and accident investigation*. Charles C Thomas Publisher.
- Brick J. and Bennett. W. (2017). Alcohol calculations in emergency and forensic medicine. *Journal of Addiction Medicine and Therapeutic Science*, 3(3): 024–029. DOI: <http://doi.org/10.17352/2455-3484.000022>
- Brick, J., Wallen, M. and Lorman, W. (2012). *Interaction of alcohol with medications and other drugs*. Haworth Press, Taylor & Francis Group, pp. 527–564.
- Fell, J. and Hertz, E. (1993). The effects of blood alcohol concentration on time of death for fatal crash victims. *Alcohol, Drugs and Driving*, 9(2): 97–106.
- Hart, E., Vikingsson, S., Winecker, R. et al. (2023). Performance of hair testing for cocaine use – Comparison of five laboratories using Blink reference specimens. *Journal of Analytical Toxicology*, 47(2): 154–161.
- Johnston, L. D., O'Malley, P. M., Bachman, J. G., and Schulenberg, J. E. (2011). *Monitoring the Future national survey results on drug use, 1975–2010: Volume I, Secondary school students*. Ann Arbor: Institute for Social Research, The University of Michigan.
- Kaufman, M., Chiu, T-M., Mendelson, J., Woods, B., Mello, N., Lukas, S., Fivel, P. and Wighton, L. (1994). In vivo proton magnetic resonance spectroscopy of alcohol in Rhesus monkey brain. *Magnetic Resonance Imaging*, 12(8): 1245–1253, Elsevier Science Ltd.
- Kaufman, M., Chiu, T-M., Mendelson, J., Woods, B., Teoh, S., Eros-Sarnyai, M., Mercer, G. and Mello, N. (1996). Brain alcohol detectability increase with repeated administration in humans: A proton spectroscopy study. *Magnetic Resonance in Medicine*, 435–440.
- Kraus, J., Morgenstern, H., Fife, D., Conroy, C. and Nourjah, P. (1989). Blood alcohol tests, prevalence of involvement and outcomes following brain injury. *American Journal of Public Health*, 79(3): 294–299.
- O'Malley, P. and Johnston, L. (2007). Drugs and driving by American high school seniors 2001–2006. *Journal of Studies on Alcohol and Drugs*, 68: 834–842.
- Pounder, D. and Jones, G. (1990). Post-mortem drug redistribution – A toxicological nightmare. *Forensic Science International*, 45(3): 253–263.
- Ropero-Miller, J., Heustis, M and Stout, P. (2012). Cocaine analytes in human hair: Evaluation of concentration ratios in different cocaine sources, drug-user populations and surface-contaminated specimens. *Journal of Analytical Toxicology*, 36(6): 390–398.
- Scholz, C., Quednow, B., Herdener, M. et al. (2019). Cocaine hydroxymetabolites in hair: Indicators of cocaine use versus external contamination. *Journal of Analytical Toxicology*, 43(7): 545–552.

- Suffoletto, B., Anwar, A., Glaister, S., and Sejdic, E. (2023). Detection of alcohol intoxication using voice features: A controlled laboratory study. *Journal of Studies on Alcohol and Drugs*, 84: 808–813.
- Ward, R., Flynn, T. and Miller, P. (1982). Effects of ethanol ingestion on the severity and outcome of trauma. *American Journal of Surgery*, 144: 153–157.
- Watson, P. E. (1989). Total body water and blood alcohol levels: Updating the fundamentals. In K. Crow and R. Batt (Eds), *Human metabolism of alcohol* (Vol. 1): *Pharmacokinetics, medicolegal aspects, and general interest*. Boca Raton, FL: CRC Press, pp. 41–58.
- Welch, R.D., Todd, K. and Krause, G. S. (1991). Incidence of cocaine-associated rhabdomyolysis. *Annals of Emergency Medicine*, 20: 154–157.

Index

- ABCD (Adolescent Brain Cognitive Development study) 214
- acetaldehyde 143
- action potential 56–8, 62–3, 88
- ADD (attention deficit disorder) 125
- addiction 47; definitions 247–50;
 - DSM-5 criteria 250; neurochemical dysregulation 250–3; relapse 257; reward pathways 252–4; treatment 254–6; withdrawal 250–1; additive drug effects 37
- adenyl cyclase 58
- ADH (Alcohol dehydrogenase) 143
- ADHD (attention deficit hyperactivity disorder) 115
- Adolescent Brain Cognitive Development study (ABCD) 214
- agonists 63, 78, 170, 172, 185
- akathisia 111
- alcohol 132; alcohol use disorder (AUD) 135–6; calculation of BAC; detection and measurement 144–7; dependence and tolerance 154, 157; epidemiology of alcohol use in USA 136–7; medical consequences 157–61; accidental injuries 157–8; cancer 159; deaths (various) 159, 164; Fetal Alcohol Spectrum Disorder (FASD) 162–3; forensic considerations 163–4; heart disease 159–60; injury outcome 157–8, 164; liver disease 161–2; organ and tissue damage 159; overdose 158–9; stroke 160–1; suicide 158; withdrawal 161–2; pharmacodynamics (neuropharmacology of alcohol) 147; biobehavioral effects of alcohol 148–51; alcohol, divided attention and motor vehicle operation 151–4; visible intoxication 149, 154; relative risk for injury 154–6; pharmacokinetics: absorption 137–41; distribution 141–2; gender differences 142; serum 282–3; social drinking 135; types of alcohol (ethyl, isopropyl, methyl) 132–4
- alcohol dehydrogenase (ADH) 143
- alcohol use disorders 135–6
- alcohol use, gender differences 137
- alcohol use, in US 136–7
- Alcoholics Anonymous (AA) 254
- Alzheimer's 204, 241, 262
- anaphylactoid reaction 182
- anhedonia 125

- animism 226
- antagonists 38, 63
- anti-cholinergic side effects 110
- antidepressants 66; forensic
 - considerations 80; frequently prescribed 76; history of development 70–1; lithium 72; medical consequences 77–8; monoamine oxidase inhibitors (MAOIs) 71; neuropeptides 74; SNRIs (selective norepinephrine reuptake inhibitors) 73; SSRIs (selective serotonin reuptake inhibitors) 73; stimulants 73; tolerance and dependence 78–9; tricyclic antidepressants 72
- antipsychotics: absorption, distribution, metabolism pharmacokinetics 101–2; history of antipsychotic medications 97–9; pharmacology of antipsychotics 101–2; atypical antipsychotics 102–4, 108; brain dopamine imbalance 102, 104; dopamine pathways 106–7; brain monoamines 105; dopamine agonists 105; forensic considerations 112; major categories of antipsychotics 103; medical consequences 109–12; schizophrenia and serotonin 108–9; typical antipsychotics 102–3; psychosis 99; signs and symptoms of schizophrenia 100–1
- anxiety 82–96; disorders and biobehavioral symptoms 84; pharmacological treatment 85–6, 92–3
- anxiolytics (anti-anxiety medications) 85–6, 92–3; biobehavioral effects: addiction 93–4; medical consequences 93; toxicity 94–5; ataxia, mood 91; insomnia; motor disorders; seizures 90–1; motor vehicle operation and related tasks 91; forensic considerations 95–6; guidelines for treatment 85–6, 92–3; pharmacodynamics 88–90; pharmacokinetics 87
- Aristotle 11
- asthma 211
- ataxia (impaired muscle coordination) 91
- Attention deficit disorder (ADD) 125
- Attention deficit hyperactivity disorder (ADHD) 115
- atypical antipsychotics 103, 108, 111
- BBB Model of Drug Action 7–10
- Behavioral Allocation Disorder 255
- beta (Widmark) 143
- beta-endorphins 59, 274
- binge drinking 2, 135–6
- biobehavioral markers 262; applied pharmacology 285–91; detection and measurement of drugs: blood 282–3; breath 282–3; hair 283–4; serum 282–3; urine 283–4; detection windows for drug use 266; drug interactions 292–4; drug tests as markers 264–6; forensics 280 (see individual drugs); postmortem toxicology 294–5 (see individual drugs); scope of the problem 281; state markers: 5-HTOL 271; acetaldehyde 270–1; AST (SGOT) 268; Beta-hex 269–70; CDT 269; EtG 271; FAEE 271; GGT 268; MCV 268; PEth 269; salsolinol 272; TSA 270; state vs trait markers 267–72; traditional markers 263–4; trait markers: adenylyl cyclase 274; beta-endorphin 274; dopamine 274; epigenetics 272–273; GABA 274; proteomics 272; serotonin 275
- bioelectric brain 13
- biogenic amines 60
- biological pumps 56
- biopsychosocioeconomic 247
- blood brain barrier 30–1
- brain, functional anatomy 49

- Broca, Paul 14
bruxism 127
- Cajal, Ramón y 13–4
Cannon, Walter B. 15–6
catecholamines/norephenephine,
 dopamine 69, 117
catecholamines 69
CBT (Cognitive Behavioral Therapy)
 85
central nervous system (CNS) 40, 41
cerebellum muscle movements 46
choreiform movement 126
chroming 192, 195
cirrhosis 162
coca (*Erythroxylum coca*) 116
coca leaves 114
Coca-Cola 115
Cognitive Behavioral Therapy (CBT)
 85
coke bugs 126
cold turkey 184
crack-eye 127
crack-dancing 126
cranial nerves 51–2
- Darwin, Charles 83
depression 66; definition, types
 and characteristics 66–8; role of
 norepinephrine 70
Descartes 11
dietary precursors, neurotransmitter
 61
DIP-C 148, 150–1
dose-response 33–4
driving, see specific drugs
driving, motor vehicle and related
 behaviors (see individual drugs)
drug efficacy 34–5
drug interactions 294–5
drug terminology 4
drug testing 263–5; see individual
 drugs
Drugs/Medications:
 Abilify (aripiprazole) 103, 108
 Adderall (amphetamine) 2, 115
 alprazolam (Xanax) 90, 93, 95
 amitriptyline (Elavil) 72, 76
 amoxapine (Asendin) 76
 amphetamine 115, 120, 122
 Anafranil (clomipramine) 76
 antibiotics 1
 anticonvulsant 90
 antidepressants, table 76
 aripiprazole (Abilify) 103, 108
 Asendin (amoxapine) 76
 Ativan (lorazepam) 86, 90
 atomoxetine (Strattera) 76
 bath salts 118
 benzodiazepines 86–90
 beta-blockers 85
 bupropion (Wellbutrin, Zyban)
 75–6, 92
 BuSpar (buspirone) 92
 buspirone / BuSpar 92
 caffeine 118–9, 122, 124–5
 cannabidiol (CBD) 203–4
 cathinone (Khat) 70, also see page
 118
 CBD (Cannabidiol) 203–4
 Celexa (citalopram) 76, 92
 chlordiazepoxide (Librium) 86,
 93, 95
 chlorpromazine (Thorazine) 98,
 102, 103
 chlorprothixene (Taractan) 103
 cimetidine (Tagamet) 143
 citalopram (Celexa) 76, 92
 clomipramine (Anafranil) 76
 clonazepam / Clonazepine
 (Klonopin) 93
 clorazepate (Tranxene) 86, 93
 clozapine (Clozaril) 103, 108–9
 Clozaril (clozapine) 103, 108–9
 cocaeethylene 121–2, 124
 cocaine 115, 120–1
 codeine 173
 crack 120, 125–6
 crack-cocaine 120
 Cymbalta (duloxetine) 73
 Dalmane (flurazepam) 90
 Demerol (meperidine) 175
 desipramine (Norpramin) 72, 76
 desvenlafaxine (Pristiq) 73, 76

- Desvrel (trazodone) 75–6
 Dexedrine (dextroamphetamine) 122
 dextroamphetamine (Dexedrine) 122
 diazepam (Valium) see 85–93
 Dimethoxy-4-methylamphetamine (DOM) 230
 Dimethyltryptamine (DMT) 230
 DMT (Dimethyltryptamine) 230
 DOM (Dimethoxy-4-methylamphetamine) 230
 doxepin (Sinequan) 76
 dronabinol (Marinol) 211, 215
 duloxetine (Cymbalta) 73
 Dramamine 26
 Effexor (venlafaxine) 75–6
 Elavil (amitriptyline) 72, 76
 Eldepryl (selegiline) 71
 Equanil (meprobamate) 92
 Equanil/Miltown 92
 escitalopram (Lexapro) 76, 92
 ethyl alcohol see 132–4
 fentanyl 176–7, 183
 fluoxetine (Prozac) 73, 76, 92
 fluphenazine (Prolixin) 103
 flurazepam (Dalmane) 90
 fluvoxamine (Luvox) 73, 76
 Geodon (ziprasidone) 103, 108
 Haldol (haloperidol) 103, 109
 haloperidol (Haldol) 103, 109
 hashish 202
 heroin 174
 hydrocodone 172, 175, 180
 imipramine (Tofranil) 72, 76
 invega (Paliperidone) 108
 iproniazid 70
 isocarboxizid (Marplan) 71, 76
 isopropyl alcohol (rubbing alcohol) 132–134
 K2/Spice 204, 209
 ketamine 75, 228–9, 232, 234
 Khat (cathinone) 70, also see page 118
 Klonopin (clonazepam/Clonazepine) 93
 Laudanum 171
 Lexapro (escitalopram) 76, 92
 Librium (chlordiazepoxide) 86, 93, 95
 Lidocaine 115
 lithium 72–3
 lithium salts 72–3
 lorazepam (Ativan) 86, 90
 loxapine (Loxitane) 103
 Loxitane (loxapine) 103
 LSD (lysergic acid diethylamide) 227
 ludiomil (Maprotiline) 72
 Luvox (fluvoxamine) 73, 76
 lysergic acid diethylamide (LSD) 227
 MAOIs 108
 Maprotiline (ludiomil) 72
 Marinol (dronabinol) 211, 215
 Marplan (isocarboxizid) 71, 76
 MDMA (methylenedioxymethamphetamine) 115, 226–7, 229
 Mellaril (thioridazine) 103
 meperidine (Demerol) 175
 Meprobamate 92–3
 mescaline (Peyote) 228
 methadone 175
 methamphetamine 115, 122
 methanol 134
 methedrine 122
 methyl alcohol see 132–4
 methylenedioxymethamphetamine (MDMA) 115, 226–7, 229
 methylphenidate (Ritalin) 73, 122
 mianserin (Tolvon) 76
 Miltown (meprobamate) 92
 mirtazepine (Remeron) 76
 Mogadon (nitrazepam) 90
 naloxone (Narcan) 181
 naltrexone (ReVia) 180
 Narcan (naloxone) 181
 Nardil (phenelzine) 71, 76
 Navane (thiothixene) 103
 nitrazepam (Mogadon) 90
 nitroglycerin 26
 Norpramin (desipramine) 72, 76
 nortriptyline (Pamelor) 76
 novocain 115

- olanzapine (Zyprexa) 103, 108
- olanzapine plus fluoxetine (Symbyax) 108
- Orap (pimozide) 103
- orexin 60
- oxazepam (Serax) 86
- oxycodone (Oxycontin) 175
- paliperidone (Invega) 108
- Pamelor (nortriptyline) 76
- Papaverine 173
- Parnate (tranylcypromine) 71, 76
- paroxetine (Paxil) 73, 76, 92
- Paxil (paroxetine) 73, 76, 92
- pentazocine (Talwin) 180
- Percodan 175
- perphenazine (Trilafon) 103
- Peyote (mescaline) 228
- phenelzine (Nardil) 71, 76
- phenylethylamine 60, 105
- pimozide (Orap) 103
- Pristiq (desvenlafaxine) 73, 76
- procaine 115
- Prolixin (fluphenazine) 103
- protriptyline (Vivactil) 76
- Prozac (fluoxetine) 73, 76, 92
- psilocybin 228
- quetiapine (Seroquel) 103, 108
- ranitidine (Zantac) 36
- Remeron (mirtazepine) 76
- reserpine (Serpasil) 98
- ReVia (naltrexone) 180
- Risperdal (risperidone) 103, 108
- risperidone (Risperdal) 103, 108
- Ritalin (methylphenidate) 73, 122
- Selegiline (Eldepryl) 71
- Serax (oxazepam) 86
- Seroquel (quetiapine) 103, 108
- Serpasil (reserpine) 98
- sertraline (Zoloft) 73, 76, 92
- Sinequan (doxepin) 76
- Stelazine (trifluoperazine) 103
- stimulants 73
- Strattera (atomoxetine) 76
- Suboxone 187
- Symbyax (olanzapine plus fluoxetine) 108
- Tagamet (cimetidine) 143
- Talwin (pentazocine) 180
- Taractan (chlorprothixene) 103
- THC (delta-9-tetrahydrocannabinoid) 202
- thebaine 173
- theobromine 118
- thioridazine (Mellaril) 103
- thiothixene (Navane) 103
- Thorazine (chlorpromazine) 98, 102–3
- Tofranil (imipramine) 72, 76
- Tolvon (mianserin) 76
- Tranxene (clorazepate) 86, 93
- tranylcypromine (Parnate) 71, 76
- trazodone (Desvrel) 75–6
- tricyclic antidepressants 72
- trifluoperazine (Stelazine) 103
- Trilafon (perphenazine) 103
- Valium 86; also see 85–93
- Valium (diazepam) 86, 93
- venlafaxine (Effexor) 75–6
- Vicodin 175
- Vivactil (protriptyline) 76
- Wellbutrin (Zyban) 75–6, 92, 242–3, 256
- Xanax (alprazolam) 90, 93, 95
- Zantac (ranitidine) 36
- zimetidine (SSRI) 74
- ziprasidone (Geodon) 103, 108
- Zoloft (sertraline) 73, 76, 92
- Zyban (bupropion) 75–6, 92, 242–3, 256
- Zyprexa (olanzapine) 103, 108
- DSM-V 3, 135
- dystonic reactions 111
- edema, pulmonary 182
- empathogens (entactogens) 227
- endocannabinoid 206
- endogenous: depression 68; opioids 175, 178; benzodiazepines 88; see 252
- endorphins, enkephalin 178
- entactogens (empathogens) 227
- epigenetics 272–3
- EPSPs (excitatory post synaptic potentials) 62

- excitatory post synaptic potentials (EPSPs) 62
- extrapyramidal side effects 110–2
- extrapyramidal system, effect of antipsychotics 110
- Fick's Law 138
- fight or flight response 85
- first messengers 57
- first-order kinetics 144
- forensic considerations (see individual drugs)
- formic acid 293
- functional neuroanatomy 40–52;
 - autonomic nervous system, peripheral nervous system (PNS); somatic nervous system 40–1;
 - basal ganglia 50; brain cortex 42–6; cerebellum 46; subcortical structures 46–8; cerebellum and brainstem 46–4; classification of neurons 42–3; cranial nerves 41, 51–2; limbic system 49–50; nervous system; parasympathetic; sympathetic 41; pituitary gland 50; ventricles 50–1
- GADH (Gastric alcohol dehydrogenase) 142
- Gage, Phineas 14
- Galvani, 13
- gastric alcohol dehydrogenase (GADH) 142
- gastric reflux 21
- glaucoma 211
- glia 54–5
- Golden Age of Pharmacology 2, 5
- gynecomastia 109
- gyri 42
- hair testing 267, 283–4
- half-life 31–3
- hallucinogens 225; biobehavioral effects 231–2; common hallucinogenics 228–9; forensic considerations 236; history of use 226–7; medical consequences 233–5; medical use 232–3; pharmacokinetics 229–31; pharmacology 231; slang terms 227–9; tolerance and dependence 235–6
- Harm Reduction Model 255
- Harrison Narcotic Act 115, 172
- Hebb, D.O. 16
- hepatic encephalopathy 161–2
- hepatitis 162
- histamine 60
- Hobbes, Thomas 12
- Hoffman, Albert 227
- homeostasis 16, 41, 48–9
- Hume, David 12
- hydrophilic 28–9
- indolamines 225
- inhalants 25, 191; absorption, administration and distribution 193; abuse and biobehavioral effects 193–4; commonly used inhalants 192; dependence and tolerance and 194; forensic considerations 196; history of inhalant problem use 192; medical consequences 195
- inhibitory post synaptic potentials (IPSP) 62
- insufflation 26, 119–20, 127
- intracranial self-stimulation 17
- ions 55–6
- ion-gated neurotransmission 56–8
- IPSP (inhibitory post synaptic potentials) 62
- LD (Lethal Dose) 35
- Leary, Timothy 227
- Lethal Dose (LD) 35
- limbic system 49–50
- lipophilic 28–9
- liver disease 161–2
- lobotomies 5
- Locke, John 12
- long term potentiation (LTP) 257
- LTP (long term potentiation) 257

- MAO (monoamine oxidase) 62, 70
 MAOI (monoamine oxidase inhibitor) 63, 71
 marijuana 197; agricultural crop 198–9, 201; biobehavioral effects 207–10; CBD (cannabidiol) 203–4; driving 219; forensic considerations 218–21; hashish 200; history of use 200–2; laboratory tests 220–1; medical consequences 212–6; medical uses 210; neuropharmacology 206; pharmacokinetics 205; plant identification 198–9; slang terms 199; synthetic cannabinoids 204; tolerance and dependence 217–8
 MDS (mesolimbic dopamine system) 18
 mead 2
 membrane pumps 56
 meth mouth 127
 mind-body dichotomy 11
 miosis (pupil constriction) 264
 moderate use, binge drinking, problem drinking 3, 135, 270
 monoamine oxidase (MAO) 62, 70
 monoamine oxidase inhibitor (MAOI) 63
 Morpheus 171
 Müller, Johannes 13
 mydriasis (pupil dilation) 74, 264
- Narcotics Anonymous (NA) 254
 Neuroleptic Malignant Syndrome 111–2
 neurons 54
 neuropeptides 73
 neurophysiology: action potentials 56–8; dietary sources for neurotransmitter manufacture 60–1; functional activity of neurotransmitters 63–4; gated and non-ion gated neurotransmission 56–68; glia; neurons; neurotransmission 54–5; ions 55; neurotransmitters and identified functions 59–60; postsynaptic and presynaptic receptors 62; synapses 55
 neurotransmitters 59–60
 nicotine 238; dependence and tolerance 242–3; forensic considerations 244–5; history of use 239; medical consequences 234–4; pharmacokinetics 240–1; pharmacology 241
 NIDA panels 265
 norepinephrine, theory of depression 70
 norepinephrine 60
 nuclei 54–5
 nystagmus 263–4
- obsessive-compulsive disorder 254
 Olds, James 17
 opioids 170; dependence, tolerance and withdrawal 184–5; detoxification 185–7; endogenous opioids (endorphins and enkephalins) 178; forensic considerations 187–8; history of opioid use 170–1; methadone and driving 188; natural opiates (opium, codeine, morphine) 173; pharmacodynamics: biobehavioral effects of opioids 181; medical uses and consequences 182–4; opioid receptors 180; pharmacokinetics: absorption, administration, distribution and metabolism) 178–80; relative potency 176; semi-synthetic opioids (heroin, oxycodone, Oxycontin, hydrocodone) 174–5; synthetic opioids (methadone, Tramadol, fentanyl) 177
- Papez circuit 16
 Parkinson's disease 5, 61, 107, 257
 Penfield, Wilder 14
 peptides (opioid) 60
 peripheral nervous system (PNS) 40–1
 peristalsis 138, 140

- pharmacodynamics 36–8
- pharmacodynamics (see individual drugs); Additive, antagonism, potentiated, synergistic 37–8
- pharmacokinetics (see individual drugs); blood brain barrier 30–31; distribution, total body water 28–29; dose-response curve 33–34; drug interactions 35; lethal and effective dose 35; elimination, drug half life 31–33; injection 27–8; oral administration 21–4; pulmonary administration 24–6; surface absorption 26–7
- pineal 12
- pituitary gland 48, 107, 178, 274
- postmortem redistribution (PMR) 295
- prenatal/fetal drug effects, antidepressants 77–8; anxiolytics 95; cocaine 127–8; alcohol 162–3; opioids 183; inhalants 195; cannabinoids 216–7; antipsychotics 112
- proteomics 272
- Pseudo Parkinsonism 110–1
- PTSD 92, 229, 233
- pulmonary edema 182
- pylorus 138, 140

- rapid detox 185–7
- rapid eye movement (REM) 90
- reactive depression 68
- relative risk, see specific drugs
- reward pathways 17
- rhabdomyolysis 195

- Schildkraut, Joseph 70–1
- schizophrenia 61, 212
- schizophrenia and Serotonin 108–9
- schizophrenia, dopamine model 102–4
- schizophrenia, MAO, endogenous psychogens, norepinephrine, dopamine 105–8
- schizophrenia, multifactor model 102

- second messengers 58
- selective norepinephrine reuptake inhibitor (SNRI) 73, 92
- selective serotonin reuptake inhibitors (SSRI) 73, 92
- serotonin 60
- serotonin syndrome 6
- serum alcohol 282
- skin-popping 28
- SNRI (selective norepinephrine reuptake inhibitor) 73, 92
- social drinking 135
- Soldier's Disease 171
- somatic and autonomic nervous system 41
- spinal fluid 50
- SSRI (selective serotonin reuptake inhibitor) 73, 92
- steatosis 162
- Sternbach, Leo 86
- stimulants 114; amphetamine vs cocaine 116; biobehavioral effects 122–4; caffeine 118–9; cathinone 118; chemical structures, molecular similarities 117; forensic considerations 128–30; history of stimulant use 114–5; medical consequences 125–8; pharmacokinetics: absorption 119; elimination 120–1; injection 120; insufflation (nasal) 119–20; pulmonary 120; pharmacodynamics and neuropharmacology: amphetamines 122; cocaethylene 121–2; cocaine 121; xanthines 118, 122; slang terms 116–7; tolerance and dependence 124
- stroke, subarachnoid, intracerebral hemorrhage and ischemic infarcts 126, 160–1
- sublingual 26
- Substance P 74–5
- synapse 55
- synergistic drug effects 36–7, 294
- synesthesia 232

tachyphylaxis 235

talcosis 183

tardive dyskinesia 5, 111

TBW (Total Body Water) 28

therapeutic index 35, 230

total body water (TBW) 28

tuberculosis 70

urine testing 265, 283

volume of distribution (VD)
28–9

water, total body 28, 142, 146

Watson, Patricia 287

Widmark, E.M. 142–143

xanthines 122

xerostomia 127