INTRODUCTION TO ADDICTION PSYCHIATRY

R. Andrew Chambers & Kevin G. Masterson

CAMBRIDGE Medicine

Introduction to Addiction Psychiatry

Introduction to Addiction Psychiatry

R. Andrew Chambers
Indiana University School of Medicine

Kevin G. Masterson
Indiana University School of Medicine

CAMBRIDGE
UNIVERSITY PRESS

Shaftesbury Road, Cambridge CB2 8EA, United Kingdom

One Liberty Plaza, 20th Floor, New York, NY 10006, USA

477 Williamstown Road, Port Melbourne, VIC 3207, Australia

314–321, 3rd Floor, Plot 3, Splendor Forum, Jasola District Centre,
New Delhi – 110025, India

103 Penang Road, #05–06/07, Visioncrest Commercial, Singapore 238467

Cambridge University Press is part of Cambridge University Press & Assessment,
a department of the University of Cambridge.

We share the University's mission to contribute to society through the pursuit of
education, learning and research at the highest international levels of excellence.

www.cambridge.org
Information on this title: www.cambridge.org/9781009501392

DOI: 10.1017/9781009501439

When citing this work, please include a reference to the DOI 10.1017/9781009501439

First published 2025

A catalogue record for this publication is available from the British Library

*A Cataloging-in-Publication data record for this book is available from the
Library of Congress*

ISBN 978-1-009-50139-2 Paperback

Contents

Preface

Addiction is a very common psychiatric disorder and brain disease that is a leading root cause of injuries, multisystem organ diseases, and premature death. Addiction strikes at the neural engine of human power: the brain system that governs and adapts our motivation that transforms our thoughts, memories, and feelings into behavioral actions. Addiction psychiatry is the oldest field within psychiatry or medicine in which physicians are formally trained as experts in the neuroscience, diagnosis, and treatment of addiction. It also remains as the only field where physicians are formally trained and board certified in *both* mental health and addictionology. Still, addiction psychiatry is quite young, being started in 1991, which speaks to how innovative and rapidly developing our field is with respect to the broader history of psychiatric neuroscience and therapeutics.

Addiction psychiatry overlaps with but is distinct from addiction medicine, which was developed into a formal training fellowship in 2016 and is open to nonpsychiatrists who typically aim to incorporate their work in addictionology into other medical specialties such as primary care or emergency medicine. But as this book reveals, addiction is a psychiatric disorder that is tightly interconnected with mental illness on neurobiological, clinical, and epidemiological levels. Additionally, addiction is optimally treated by an integration of psychotherapeutic and medication management strategies, which psychiatrists, among all physicians, are best trained to deliver. So, across the landscape of health care, addiction psychiatrists are the best prepared among all physicians to treat this devastating brain disease and its many complex comorbidities with mental illness.

Introduction to Addiction Psychiatry aims to efficiently inform the healthcare professional or scientist-in-training with the fundamental concepts of our field, highlighting what is unique and powerful about it scientifically and clinically under the larger addictionology umbrella. There are many large-volume addiction or addiction medicine textbooks

already available that serve as excellent reference books for professionals who have already chosen to enter some area of addictionology. However, these volumes are often quite expensive, physically heavy, and written as encyclopedic amalgamations of clinical and pharmacological facts compiled by a dozen or more authors writing chapters separately from one another. They typically are not focused on or dedicated to explaining the science and practice of *addiction psychiatry*, and they are not necessarily practical for young clinicians and scientists who have yet to decide about their career directions. So, this book is designed to address these gaps, working much more as an internally coherent, concept-oriented, illustrated introduction to the field that can attract and engage learners across many medical/psychiatric and scientific disciplines.

The two authors of *Introduction to Addiction Psychiatry* – one a seasoned addiction psychiatrist, neuroscientist, and fellowship director (Chambers), and the other (Masterson) a general psychiatry resident and addiction psychiatry fellow at the time of his contributions to the book – have drawn from their collective experience spanning 25 years in teaching addiction psychiatry. The audiences that helped us write this book include undergraduates, nursing students, social workers, legal professionals, medical students, residents, neuroscience graduate students, postdocs, and addiction psychiatry fellows. From this experience, we have attempted to build this book like a "greatest hits album" of our most impactful and compelling lessons, concepts, and figures, providing a rapid and yet unforgettable initiation to the translational neuroscience and practice of addiction psychiatry. As such, the book can readily be used to accompany short lecture series on addiction psychiatry for a broad scope of professional and scientific learners, especially those that may be engaged in other courses, or busy clinical or scientific rotations.

There are other innovative features of *Introduction to Addiction Psychiatry* that we designed to optimize its impact for students and trainees. First, we have organized it into five chapters that each describe addiction according to one of five fundamental criteria for how modern medicine defines any *disease*. In testing this approach in a classroom of undergrads who were quite skeptical that addiction is truly a disease, we found this strategy to be an incisive way to defeat stigma by combatting denial about its disease attributes. Universalizing the understanding of addiction as a biomedical healthcare problem that can and should be reduced through science-backed treatment – rather than being hidden,

judged, or punished as a moral failure, religious deficiency, or crime – is an imperative for all learners entering medicine and psychiatry. We also found that writing the book using the five-chapter disease criteria organization provides a strong scaffolding on which we can showcase the remarkable connectedness that exists between neurobiology, pharmacology, behavior, clinical symptomatology, and population health that is at the heart of what is really cool about addiction psychiatry. In Chapter 5, the last and largest chapter, the translational science and clinical observations accumulating through the first four chapters culminate in a tour-de-force explanation of knowledge and methods that addiction psychiatrists deploy for saving lives and propelling suffering patients and families into solid recovery trajectories.

Second, this book represents the first addiction psychiatry textbook that explains and integrates the emerging *neuroscience* of addiction psychiatry with the *practice* of addiction psychiatry. This theme, running throughout the book but elaborated on most fully in Chapter 4, establishes the area of basic neuroscience that is foundational to addiction psychiatry in terms of describing how addiction and mental illness are etiologically, developmentally, neurobiologically, and clinically intertwined and bidirectionally interactive. This science indicates a strong rationale and need for growing the field of addiction psychiatry as a new core of general psychiatry and public health, while also, hopefully, inspiring a reinvestment in neuroscience, training, and clinical practice that rejects the siloes and fragmentation that have so adversely and artificially separated mental health from addictionology. As made possible by this basic neuroscience foundation, the book also fortifies the essential identification of addiction psychiatry with excellent integrated dual-diagnosis treatment. In this care model, which addiction psychiatrists are the best trained to lead, patients are not treated artificially or inaccurately as mono-diagnostic disease targets. Instead, they are understood and treated as they often are – as people with extremely complex combinations of multiple addiction and mental illness syndromes, which are not static but can evolve drastically over time. *Introduction to Addiction Psychiatry* thus provides learners with a coherent, unified translation between brain science, training, practice, and service delivery that are the pillars of our field.

Third, and finally, this book introduces learners to many core concepts that are fundamental to understanding psychiatric neuroscience, behavior, and their many fascinating interconnections. This highly accessible

"reveal" for students is necessary and made possible through the work of explaining addiction as disease of motivation. Because motivation is the engine of human brain power that transforms our thoughts, memories, and feelings into behavioral action, the neuroscience of addiction psychiatry as covered in this book can also serve as an introductory general primer for how our brains are built, how they work, and how they can get sick through addiction and mental disease. By extrapolation, the neuroscience of addiction psychiatry can be expected to have great relevance to the advent of artificial intelligence and autonomously behaving robots, which have been informed by and seek to emulate the functions of biologically sentient self-motivated beings. Similarly, the practice of addiction psychiatry is rapidly becoming the key field of medicine and psychiatry that is best positioned to grapple with our interactions with the internet and social media. For all the informational benefits this technology brings, it is also capable of generating mass misinformation, delusion, adverse population behavior, technology addictions, widespread access to addictive psychoactive drugs, and social–emotional harms as public health "side effects." Addiction psychiatry is uniquely positioned to help protect us humans from these current and future harms.

This book is dedicated to building the future of addiction psychiatry and all the doctors, multidisciplinary healthcare professionals, and scientists that will join this field in the years to come. Above all, it is dedicated to improving the lives and well-being of people and families everywhere in the world who may be suffering with addiction and mental illness.

1

Population Impact: Epidemiology

Learning Points

- **Addiction is a highly prevalent and dangerous psychiatric illness and brain disease.** It can result in massive harm to an individual's physical and mental health, their occupational and social function, their families, and social networks.
- **Addiction psychiatry is a healthcare field led by physicians who are uniquely cross-trained, and board-certified in the neuroscience, diagnosis and treatment of *both* mental illness and addiction.** Addiction psychiatrists are expertly qualified to treat these diseases whether they are encountered as stand-alone disorders or – as they most commonly occur – as complex combinations of comorbid illnesses (i.e., "**dual diagnosis"**).
- **Addiction is the leading root cause of morbidity and mortality in the United States**. This is because, when untreated, addiction leads to so many other injuries and disorders of the mind and body that are incredibly destructive and imminently lethal.
- **Stigma has limited the healthcare system from appropriately recognizing, preventing, and treating addiction as a disease, even as it squarely fits five core criteria for what defines**

a disease. Addiction is a disease that (1) has a massive yet uneven public health impact; (2) is characterized by a well-defined symptomatology; (3) involves specific neuroanatomical substrates and a complex pathophysiology; (4) is exacerbated by biologically active genetic, environmental, and neurodevelopmental risk factors; and (5) is measurable, reduceable, and remittable through the expert use of reliable and effective diagnostic tools and biologically active treatment strategies.

- **Addiction is disproportionally highly prevalent in people with mental illness and those exposed to addictive drugs in adolescence – all as a reflection of its underlying neurobiology.** However, there are many biologically active disease risk factors for addiction and most people carry some risk of becoming addicted. Some of the most well-educated, intelligent, and financially advantaged people in our society (e.g., physicians) are susceptible to the disease.

Introduction

Addiction is a brain disease that afflicts about one in five adults and is a leading root cause of injuries, illnesses, and mortality in the United States. In modern society, addiction, often comorbid with mental illness, is the leading killer of people who don't die in old age. This stark reality is not well appreciated, or often taught, in medical schools. **Stigma**, a widely held social attitude of judgment, inferiority, and disgrace aimed toward people with certain attributes or diseases, is frequently leveraged against people with addictive disorders and mental illness. Lack of treatment infrastructure, paucity of well-trained professional workforce, and insufficient insurance coverage for behavioral health disorders all play a role in the underrecognition of addictive disorders (and its harmful relegation to the criminal justice system), adversely contributing to its morbidity and mortality. Diagnostic indications for medical or surgical hospitalizations and causes of death are often attributed to proximal causes (e.g., cardiovascular disease, malignant carcinoma, cerebrovascular disease, infections, accidents, and so on) rather than to the chronic underlying brain-based behavioral disorders that often lead to these conditions, such as addictions to nicotine, stimulants,

alcohol, and opioids. However, recent public health calamities, like the **iatrogenic** (meaning disease *caused* by the improper/harmful delivery of health care) epidemic of opioid addiction, have increased awareness within the medical community that addiction diagnosis and treatment must become a high priority in mainstream medical and psychiatric care.

A longstanding lack of understanding about the scope and nature of addiction as a disease (covered in Chapters 1 and 2), its neurobiology (Chapter 3), its connection with mental illness (Chapter 4) and its treatability (Chapter 5) – even within medical and psychiatric education – has contributed to the healthcare system's lackluster tradition in taking responsibility for identifying, preventing (or avoiding causing), and treating it to the extent we are capable of. The primary goal of this book is to provide the medical/psychiatric trainee and brain-behavioral health scientist with a relatively concise yet in-depth understanding of what addiction is, in all its five core dimensions as a *disease process*. In covering these illness dimensions, this book serves as an introduction to the field of addiction psychiatry. As such, it aims to integrate scientific and clinical information into one coherent framework of knowledge that will serve as a foundation on which a larger and more impactful addiction psychiatry workforce, treatment, training, and research infrastructure can be built as a core domain of psychiatry and public health.

What Is Addiction Psychiatry?

Addiction psychiatry, like its closely allied field addiction medicine, is focused on the diagnosis and treatment of addictions and various related substance use disorders (e.g., withdrawal syndromes). However, addiction psychiatry is uniquely and expertly focused on the neuroscience and treatment of the full spectrum of *both* mental health and addiction disorders, whether they occur as standalone or comorbid conditions. As such, addiction psychiatry is the only American Board of Medical Specialties (ABMS)-defined field of medicine that requires formal training in both psychiatry and addictionology, which in the US is accomplished via (a) the completion of a four-year general psychiatry residency program and (b) a year of addiction psychiatry fellowship training. In this way, addiction psychiatry is actually a broader and deeper scope of expertise in comparison to what general psychiatry

training alone provides, allowing addiction psychiatrists to treat a much wider array of patients and comorbid diagnostic conditions, with higher levels of training spanning neuroscience, diagnostics, psychotherapeutics, and pharmacology. It is thus perhaps a misnomer to regard addiction psychiatry as a subspecialty of psychiatry when the training actually amplifies and broadens one's diagnostic and treatment capability. Addiction psychiatry can be understood as *advanced* training in general psychiatry, with an emphasis on enhancing the expert management of patients with complex combinations of multiple addictions and mental illnesses, and for leading multidisciplinary treatment teams that make this care more impactful. Because patients with complex comorbidities of mental illness and addictions (i.e., "**dual-diagnosis"** patients) are so common and mainstream (due to *biological* reasons, reflecting fundamental design features of the mammalian brain described in Chapter 4), the unmet need for more addiction psychiatrists (who can integrate our highly fragmented and siloed systems of addiction versus mental health care) is immense.

Addiction medicine fellowship training and certification, in contrast to addiction psychiatry fellowship training, accepts both psychiatrists and nonpsychiatrists (e.g., family medicine doctors, neurologists, internists, surgeons, emergency medicine doctors, anesthesiologists, Ob-Gyn doctors, and so on). Also, unlike addiction psychiatry, addiction medicine certification does not require formal fellowship training (only a certification exam and letters of support). However, in the coming years, addiction medicine will likely transition to the more formal and rigorous training standards of addiction psychiatry certification, requiring a year of formal fellowship training as a subspecialty of physical medicine and rehabilitation. In general, psychiatrists who go on to train in either addiction psychiatry or addiction medicine fellowships are similarly equipped to provide integrated addiction and mental health care (i.e., integrated dual-diagnosis care, as an addiction psychiatrist), whereas nonpsychiatrists who pursue addiction medicine provide addiction treatment for patients in a way that is more limited in terms of providing psychiatric expertise or integration with mental health, yet integrated with their particular lines of medical practice (e.g., the Ob-Gyn physician who prescribes buprenorphine to her pregnant patients).

The unique expertise of addiction psychiatrists in providing care and leading teams that fully integrate mental health and addiction treatment is an important capability because (a) the majority of patients with

significant mental illness have addiction comorbidity of some kind, and (b) addiction diseases routinely produce or worsen mental illness. Split care, where patients may be seeing one doctor for addiction treatment and another for psychiatric care in two different systems, at two different locations, is not as effective or efficient (for either the healthcare system or patients) and should be avoided if possible. As we will describe in Chapter 5, addiction psychiatrists are uniquely trained to provide care that avoids this split by providing and leading **integrated dual-diagnosis care**. This kind of integrated care not only allows for more coherent treatment planning, but it better supports *longitudinal continuity of care* and stronger therapeutic relationships; the addiction psychiatrist is able to support recovery even as patients progress through different phases of mental illness and/or addiction symptomatology.

For primary care doctors and other nonpsychiatrists attempting to practice behavioral healthcare in the form of addiction medicine, there are several boundary hazards and pitfalls that exist that psychiatrists, by nature of their practices and their training, are better equipped to avoid. These hazards include performing invasive physical examinations on patients who have significant histories of sexual-emotional trauma or having personal relationships (friendships or romantic) outside of the professional practice-based relationship with patients. Psychiatrists are trained in **boundary awareness**, to never have *personal* emotional or *sexual* relationships with patients they are treating (or have treated in the past), and they generally do not perform examinations of private/erogenous body zones. These guard rails serve to protect patients and psychiatrists from nontherapeutic, harmful, or exploitative directions that treatment can take in the context of (1) establishing quite intimate therapeutic alliances and familiarity with the mental life and emotions of patients; (2) the prescribing of mind-altering, controlled drugs; (3) the presence of certain mental illnesses that can make certain patients extremely vulnerable (e.g., to eroticized interactions); and (4) the considerable power differential that often exists between psychiatrists/therapists and their patients.

In addition to core training in maintaining boundary awareness, four years of general psychiatry training (as a prerequisite for pursuing addiction psychiatry training) also encompasses education and training in psychiatric neuroscience (e.g., neuroanatomy and cognitive/affective neuroscience), the diagnosis and management of personality disorders,

and the science, theory, and delivery of various psychotherapies and pharmacotherapies. Personality disorder symptoms, which are not unusual in patients with addictions (and can be amplified by co-occurring addictions) can produce chaotic effects in a general medical practice, in doctor–patient relationships, and for physician's decision-making, especially for doctors who are untrained in diagnosing and managing them. At the same time, understanding what psychotherapy is, how to deliver it, and how to supervise other professionals who are delivering it, are important skills for effective addiction treatment. Psychiatrists are the only physicians that are required to have formal training in psychotherapy. For optimal results, psychotherapies should often be integrated with medication management in the treatment of addictions and comorbid mental illness. Thus, psychiatrists entering addiction psychiatry have a significant foundational advantage in being already trained in key skill sets needed for expert practice in addictionology, whereas nonpsychiatrists entering addiction medicine must attempt to fill these training gaps in their one-year fellowship, or in other ways outside of what psychiatric residency training provides.

Given the considerable overlap between the allied fields of addiction psychiatry and addiction medicine, this book can serve as a useful primer for both fields, albeit through the lens of addiction psychiatry which places more emphasis on (i) the **translational neuroscience** of addiction (i.e., explaining how the brain science of addiction generates clinical–human-level phenomena); the (ii) **integrated neurobiology of mental illness and addiction** (i.e., explaining how mental illness and addiction are interconnected biologically and clinically); and (iii) the deployments of **integrated treatments** (e.g., using combinations of both psychotherapies and medications) to drive recovery and disease remission.

Addiction Is a Brain Disease

A usual stumbling block in understanding addiction for the public and even medical professionals is the challenge in appreciating and accepting its true nature as *a disease*. This lack of understanding is a major contributor to stigma, which infiltrates even the healthcare system, causing it to be uninterested, deficient, or incompetent in adequately diagnosing and treating addiction. Stigma, occurring in the form of

denial that addiction is a real disease, can even contribute to a tendency of the healthcare system to sometimes *cause it*, via negligent or exploitative overprescribing of controlled drugs. Thus, in explaining addiction as a genuine biomedical condition that needs expert, science-based treatment (and not as a crime to be punished, or as a moral or religious failure of "bad apple patients"), it is important to discuss how it clearly fulfills our medical definitions and criteria for what constitutes a disease.

Taking this approach, this book will focus on addiction in terms of five core attributes, or criteria that modern medicine uses (and medical students learn) to define any given entity as a *disease*. A disease is an entity of biomedical attention that: (1) *impacts a population* of patients and has associated morbidity and mortality; (2) *is associated with reliable sets of signs, symptoms, and clinical features*; (3) is *produced by an underlying biology of altered anatomical structure and function*; (4) is *associated with a range of biologically active risk factors*; and (5) *can be reliably diagnosed and treated* by interventions that target the involved biological systems. As we introduce the reader to the field and knowledge of addiction psychiatry, this five-part definition will guide us in the content organization for the chapters of this book:

Chapter 1: Population Impact – Epidemiology. Addiction is a highly prevalent brain disease that produces extensive damage for individuals and society.

Chapter 2: Specific Symptoms Sets – Clinical Phenomenology. Addiction symptoms represent a disease of motivation that is comprehensively devastating to physical and mental health, yet strikingly similar across addictions to very different drug types.

Chapter 3: A Disorder of Anatomical Structure and Function – Neurobiology. Brain circuits that generate and adapt motivation are subject to progressive pathological changes in addictive disease as demonstrated across humans and other animal species.

Chapter 4: Biological Risk Amplification – Disease Vulnerability. Addiction disease risk is involuntary (not a simple matter of a person's choice) and is unevenly distributed in the population; it is neurobiologically associated with mental illness, adolescent neurodevelopment, and various related genetic and environmental factors.

Chapter 5: Diagnosis and Treatment – Disease Tracking, Reduction, and Remission. Addiction psychiatry uses an array of subjective and objective diagnostic tools and science-based treatment strategies to comprehensively reduce or remit additions and mental illness comorbidities.

Core Definition of Addiction

At the crux of what the Western medical tradition says a disease should entail is that it involves abnormal anatomy and functions of biological/physical (body organ) substrates. Addiction disease most directly involves pathology in brain systems that generate and control the functions of **motivation and free will**. It is perhaps because these faculties are so wrapped up into who we are and what we are capable of as human beings – and our thinking about these faculties are so tied into philosophical and religious traditions – that we have a hard time understanding them from a biomedical/scientific point of view. But to understand addiction as a disease, we must understand motivation and free will from a biomedical point of view. So, we start with these two basic definitions:

Motivation *is the brain-generated drive and sequencing of a series of goal-directed actions.*

Free will *is the brain's capacity for choosing specific actions from an array of options.*

Although motivation and free will are mediated by neurophysiological processes occurring in the brain, these concepts are more abstract and difficult to measure compared to more concretely testable abilities or functions like gait, memory, strength, urinary output, or glucose levels. For instance, someone can experience motivation toward taking several different actions all at once that is not visible to an outside observer. The observer is also not quite able to see a motivational pattern until a whole sequence of actions are acted out. At different junctures in the sequence, free will may intervene at different extents to determine the whole sequence. Where addiction comes in as a diseases process is that it represents a pathology of **compulsive motivation** that overrides other healthy motivations (choices of behavioral programs), thereby **degrading**

the faculty of free will. Human cultures have long evaluated motivation and free will through a lens of morality. However, those with addiction are not inferior to the unaffected. Addiction is not a condition where someone has an immoral or criminal free will. Rather, it is a disease process that progressively destroys free will. Mastering addiction neurobiology requires us to expand and evolve our understanding of what motivation and free will are as more than just philosophical, psychological or moral concepts, but as *neurobiologically generated products*. Objective criteria that relate to an individual's pathological motivation (in addiction) helps guide medical–psychiatric assessment of diagnosis so that treatment can always begin from a place of professional nonjudgment, with stigma removed as much as possible. The **Diagnostic and Statistical Manual (DSM)** for psychiatric disorders provides the most definitive current consensus of clinical criteria needed to make diagnoses of addiction (see Chapter 2). But as a foundation for helping us link the clinical phenomenology of addiction with the neuroscience of the disease, it is helpful to start with a very simple and yet accurate definition of addiction that boils down the DSM criteria as follows:

Addiction is a *chronic, progressive brain disease* producing pathological, involuntary growth of *compulsive motivation* (to where free will is compromised), resulting in maladaptive behaviors (e.g., drug-seeking and drug-taking) despite *the accumulation of negative consequences*.

As we will discuss in Chapters 2 and 3, addictions are **substance use disorders (SUDs)** that are very different in symptoms and biology from intoxication and withdrawal states, which are also included under the umbrella term substance use disorders (SUDs). **Intoxication** and **withdrawal** involve the relatively *acute*, pharmacological and toxicological consequences of drugs on the brain that include transient sensory, cognitive, motor, and/or emotional effects. In contrast, addiction involves a *chronic* change in motivation caused by repeated drug use, which progressively diminishes the capacity for healthy decision-making and adaptive motivation. **Behavioral addictions** (or "impulse control disorders," which addiction psychiatrists are also focused on treating) can also occur, involving reinforcers that are not strictly invoked by externally supplied chemicals, such as pathological gambling, binge

eating, compulsive shopping, shoplifting, video gaming/technology use, or pathologically impulsive–compulsive sexual activity. These impulse control disorders are often highly comorbid with drug addictions (and other mental illnesses) and share many of the clinical features and neuroanatomy as drug addictions.

Health Impact of Addiction

The morbidity (sickness and injury causing consequences of disease) **and mortality** (lethality of disease) **of addiction** is massive in modern societies. In an influential 2004 paper that opened the eyes of the medical community to how big the untreated addictions and other behavioral conditions are in all-cause medical morbidity, Mokdad et al. (2004) reported that the top three root causes of death in the United States are: (1) tobacco use; (2) poor diet/poor exercise; and (3) alcohol use. The medical mortality due to other illicit or iatrogenic addictions also ranked in the top 10. This accounting was made even before the iatrogenic opioid epidemic (c. 1995 to present), which by itself would become a leading cause of death in the US, had become fulminant.

To understand how addiction represents such a powerful cause of illness and pathways to premature death, one has to grasp how extensive, diverse, and potentially lethal the list is of secondary injuries, medical and psychiatric diseases that addictions can cause. A key to this understanding is an appreciation for how the *chronic-toxicological* nature of addiction is something that far outweighs the risks and damage of acute intoxication/withdrawal (e.g., that goes with initial use or any one episode of use). The compulsions of addiction result in years-long, incessant, heavy use that vastly increases the risk of death and disease via cumulative toxicological injury to multiple organ systems and repeated episodes of intoxication that drive injury-producing behaviors. Smoking one cigarette does not cause heart disease, chronic obstructive pulmonary disease (COPD), stroke, and cancer, but smoking one cigarette every few hours for many years almost certainly will. Similarly, chronic smoking greatly increases one's cumulative chance of dying in a house fire far beyond what smoking a single cigarette will do.

The top 10 *proximal* causes of death in the US include the usual suspects as shown in Table 1.1. These causes accounted for about 74% of all mortality in 2016. The top five causes alone accounted for 62% of mortality. It is important to consider how these *proximal* causes of death, which at face value seem to have nothing to do with psychiatric/brain-based disorders, are largely attributable to or are caused by the use of addictive substances as *root, or long-range causes* of death that lead to these proximal-medical causes expressed at the end stage. For instance, consider the #1 cause of premature death in the United States: nicotine/tobacco addiction. Per a 2014 Surgeon General report, some 500,000 deaths a year in the United States are linked to tobacco use. This tobacco-related mortality, which kills about half of all people who die before they reach the average life expectancy, mainly results from chronic use that, initially at least, only minimally impedes function or represents a health threat. A strong addictive use pattern with nicotine often develops years before negative health consequences emerge. Table 1.2 shows estimates of how many deaths, produced by four of the top five common proximal causes of death shown in Table 1.1, are actually attributable to chronic tobacco use (i.e., nicotine addiction). Chronic tobacco use also greatly amplifies the organ damage effects of diabetes while also operating as a risk factor for dementia and the progression of chronic kidney disease. Again, while tobacco provides the toxic mixture of chemicals responsible for most of the negative health effects of smoking, it is nicotine (the key addictive chemical in tobacco) that is responsible for the chronic compulsive use that produces the cumulative multiorgan toxic exposure of tobacco. Chronic second-hand smoke (resulting from living with

Table 1.1 Top 10 causes of death in the United States, 2016

1. Diseases of the heart	6. Alzheimer's disease
2. Malignant neoplasms	7. Diabetes mellitus
3. Unintentional injuries (accidents)	8. Influenza and pneumonia
4. Chronic lower respiratory diseases	9. Nephritis, nephrotic syndrome, and nephrosis
5. Cerebrovascular diseases	10. Intentional self-harm (suicides)

National Vital Statistics Report (Heron, 2018).

Table 1.2 Estimated deaths attributable to smoking tobacco, 2005–2009

Disease	Fraction of deaths attributable to tobacco (%)
Coronary heart disease and other diseases of the heart	21.4
Total cancer	48.6
Total pulmonary disease (includes COPD, emphysema, bronchitis, influenza, pneumonia)	61.7
Cerebrovascular disease	11.3
Diabetes mellitus	12.7

Surgeon General Report DHHS, 2014.

someone with nicotine addiction) also increases the risk of disease to those exposed, even if they are not directly smoking.

Now, consider another hugely popular addictive drug (even among ancient humans, more than 10,000 years ago!): alcohol. Alcohol drinking results in about 90,000 deaths annually in the US. It is also a known risk factor for multiple proximal top causes of mortality, including cardiovascular disease, cerebrovascular disease, diabetes, and liver disease. Alcohol is also an established carcinogen, leading to a significant percentage of all cancer deaths involving multiple organ systems. This carcinogenicity probably occurs by several molecular mechanisms, including its metabolism to acetaldehyde, which interferes with DNA repair.

In addition to its chronic toxicological effects on multiple body organs, alcohol also produces profound acute and long-term effects directly on the brain, which are in turn associated with an incredibly wide array of behavioral and psychiatric illness pathways that lead to severe injuries and/or death. Alcohol intoxication is a leading cause of injuries and deaths by falls, fires, water (drownings), assaults and murders, and so on, and it is a leading cause of death by overdose either as a single agent or in mixture with other drugs. About a third of deaths from motor vehicle accidents (incidents included under "unintentional injury" – the #3 top cause of death in Table 1.1) are attributable to alcohol use. Alcohol also greatly amplifies the risk of completed suicide by both its acute and

chronic psychiatric effects. While alcohol intoxicated, a person who might otherwise be only passively thinking about suicide may have that motive become **disinhibited** (i.e., increase the likelihood of being impulsively acted out). Also, with chronic use, alcohol contributes to the pathogenesis of several neuropsychiatric disorders like depression and dementia that can further amplify the long-term risk of death by accidents or suicide. Although substance use in general is associated with a 10–14× increased risk of suicide, addictions involving alcohol and opioids carry some of the highest risk, being associated with about a quarter to nearly half of all completed suicides.

The aforementioned discussion of nicotine and alcohol hasn't even considered the burden of injuries, illness, and death caused by opioids and opioid addiction. Rates of chronic opioid use has increased by three- to four-fold in the general US population over the prior three decades, as triggered and spread by the iatrogenic opioid epidemic. By 2010, a person in the US was more likely to die from an opioid-involved overdose than from a motor vehicle accident or gunshot injury (National Safety Council, 2021). By 2020, drug overdoses, often involving combinations of opioids with alcohol and/or benzodiazepines, had become the leading cause of death for Americans under the age of 50. For the first time in modern history, the life expectancy of Americans began to drop (after a century of increases), largely due to "**deaths of despair**" (overdoses and suicide associated with untreated mental illness and addiction). By comparison, the last time a multiyear decrease in US life expectancy occurred was 1915–1918 in the aftermath of World War I and the H1N1 "Spanish flu" pandemic, which infected about one-third of the world's population. Even COVID, which killed more than a million Americans from 2020 to 2022 (mostly dying over the age of 60), did not kill as many US citizens under the age of 50 as did drug overdoses and addiction. Even before a lethal outcome from opioid addiction, which may happen by any one of a very large number specific pathways besides overdose, opioid addiction can also produce or worsen a very wide range of secondary body organ diseases, injuries, and psychiatric consequences including but not limited to HIV–AIDs, endocarditis, viral hepatitis, liver cancer, sepsis, traumatic brain injury, depression, and posttraumatic stress disorder (PTSD).

So, in this brief overview of addiction's health impact, we have considered just three substances (nicotine, alcohol, and opioids) in some detail, each of which independently represents a major root cause

of many forms of injuries and secondary medical diseases that are all eventually quite lethal and expensive to treat medically and surgically. When considering these consequences as compounded further by the chronic misuse of an even wider array of addictive drugs (including cocaine, amphetamines, sedative-hypnotics, cannabinoids, inhalants, various designer drugs, and so on), it is readily appreciated how broad, deep, and frankly unparalleled addictions' overall public health impact truly is in terms of the totality of human suffering and lives lost.

Economic Impact of Addiction

The National Institute on Drug Abuse (**NIDA**: the largest National Institute of Health (NIH) section that supports research on drug addictions) has estimated that based on data from various studies spanning the years 2007–2013, the economic impact of addictions involving tobacco, alcohol, illicit drugs, and prescription opioids was reaching beyond $820 billion annually due to lost worker productivity, related criminal-justice interventions, and increased healthcare utilization. As of 2020 and later, this economic burden is likely higher still – potentially near $1 trillion a year – which would account for about 5% of the United States annual gross domestic product (GDP). Opioids alone are thought to have cost a cumulative $1 trillion from 2001 to 2017 with the annual cost still increasing. At the same time, the cost of the "**war on drugs**" (the term given to US federal and state government efforts to reduce drug use and addiction through criminalization and mass incarceration) has reached beyond $1 trillion since the 1970s, while producing no measurable desirable results, and in fact corresponding to *an increasing death toll* due to addiction in parallel with increasing per-capita rates of mass incarceration.

Decreased labor force participation (which generally doesn't count for loss of labor force due to early deaths from addiction or incarceration of addicted people) is one of the largest economic harms of drug addiction and reflects how debilitating addiction can be for individual functionality and society as a whole. Due to the widespread penetrance of and effects of addiction, particularly on young adult to middle-aged people, the workforce effects of addiction hit hardest precisely in those of prime working age (20s–40s). This depletes the ability of companies specializing in virtually all fields of services and production to hire and

invest in new and long-term employees. In the example of opioid addiction, the chronic use of both prescribed and nonprescribed opioids is elevated several-fold among unemployed men of prime working age. Even those still in the workforce who take opioids have a higher likelihood of requiring sick days, having work absences, or utilizing workers' compensation benefits. Loss or derailment of educational achievement due to addiction and extended removal or restrictions from access to employment due to criminal charges associated with addictions produce significant socioeconomic damages and worsening of educational and economic divides within the population. These trends may represent significant threats not only to economies but to the survival of democratic forms of government.

Demographic Scope and Subpopulations at Risk for Addiction

There have been hundreds of epidemiological studies of addiction and comorbid mental illnesses spanning both large and small population samples in the United States over the last 50 years. For the purposes of this chapter, we will draw mainly form the National Survey on Drug Use and Health (NSDUH) data, prepared by **SAMHSA** (Substance Abuse and Mental Health Services Administration, 2019), because (a) it provides fairly recent evidence (2018; national sample of $n = 67{,}791$) that generally agrees with trends identified elsewhere in the literature over recent decades; and (b) it also allows us to highlight some of the research design flaws that are present in this area of medical epidemiology. With that said, the reader should be aware that rates of addiction to specific drugs do wax and wane over time (somewhat like infectious disease epidemics), and they can also vary considerably by population subgroups, region, or across the urban/rural divide.

NSDUH findings from 2018 estimate that about 20.3 million people (7.4% of the US population aged 12 and over (~274 million people)) met criteria for a *substance use disorder* in the past year. Within this set, the top five substance disorders by prevalence of drug type included #1, alcohol (14.8 million, 5.4% of the population); #2, marijuana (4.4 million; 1.6%); #3, opioids (including "misused" prescription opioids and heroin;

2.2 million; 0.8%); #4 methamphetamines/amphetamines (including other "misused" prescription stimulants; 1.7 million; 0.6%); and #5 cocaine (1 million; 0.4%).

It is important to appreciate that these estimates exclude several addiction contexts or subgroups: (1) chronic use and disorders involving tobacco (estimated to be about 12–18% of the population when counting cigarettes, cigars, pipes, dipping, snuff and chewing); (2) the use of nontobacco nicotine products (vaping, e-cigarettes, nicotine gum); (3) those with addictions who are younger than 12; and (4) adults with addictions to opioids, stimulants, and/or sedative/hypnotics that they may be prescribed and taking as directed, even though they may actually have undiagnosed addictions to those drugs.

The actual percentage of the US population (age 12 years and older) meeting criteria for a substance use disorder is thus around 20% when tobacco/nicotine products are included. Notably, the fraction of the US population (12 and older) who used a particular addictive substance (spanning nicotine, alcohol, and illicit drugs) within the last month, *but not necessarily in a pattern that would meet criteria for a substance use disorder*, was 164.8 million, or 60.2% of the adult population!

Analyses that compare the fractions of the population who meet criteria for a SUD for a given drug compared to that drug's rate of overall use (i.e., use that is and is not at levels that represent addiction) can provide a way to estimate which drugs are among the most addictive in human populations. From this perspective, which estimates a given drug's relative **addiction risk or addiction potency** as a matter of how likely a person will get addicted if they experiment with it, the weight of the evidence suggests that stimulants (amphetamines/cocaine), opioids, and nicotine rank among the most addictive of all known substances. Alcohol, marijuana, and sedatives (to a large extent in this order) are moderately addictive; and the hallucinogens (e.g., LSD, psychedelic mushrooms) are least (or not at all).

Unfortunately, most epidemiological studies focused on describing rates of addictions involving illicit substances or alcohol typically exclude nicotine (and tobacco) despite its highly significant public health impact (e.g., as the most lethal of all addictive drugs in terms of total yearly death toll), and characteristic as one of the most highly addictive of all known substances. This frequent omission of nicotine from the research literature hampers understanding of overall substance disorder rates in the general

population and in certain patient groups (e.g., the mentally ill). This has led to underestimations of the overall scope and impact addiction has on society and in certain subgroups, and how these drug addictions frequently intermingle. For example, the study of Lasser et al. (2000) was among the first to show how concentrated nicotine addiction actually is in people with mental illness. This study showed that about half of all cigarettes smoked in the US are consumed by someone with mental illness, and lifetime rates of nicotine addiction were found in about 55% and 59% of those with lifetime or past month mental illness, respectively. Similarly, Weinberger et al. (2018) found that 56% of those with an illicit substance use disorder also use tobacco, while Grant et al. (2004) showed that 45% of people with alcohol dependence (i.e., alcohol addiction) also had nicotine addiction. Notably, Grant et al. also confirmed Lasser et al.'s earlier findings linking nicotine to mental illness. In Grant et al. (2004), a third of all cigarettes were found to be consumed by just 7.1% of the US population – those who also have a mental illness. At the same time, people who have nicotine addiction and a mental health history of some kind comprised about 55% of all smokers! Together, these data showed that (1) **polysubstance use disorders** (i.e., having more than one type of drug encompassed within a patient's addiction illness) is the rule and not the exception for those using illicit substances; (2) polysubstance use is present in nearly half of people suffering with alcoholism; and (3) having an addiction of any kind is the norm in half or more of people with current or history of mental illness.

The following sections will discuss substance use disorder epidemiology across various sub-groups. A range of genetic, environmental, and neurodevelopmental risk factors are typically in play to generate increased risk and penetrance of addiction disease in particular subpopulations. Often these factors co-conspire simultaneously within one subgroup or individual to greatly increase both disease risk and severity. This is particularly true in the context of adolescent/young-adult neurodevelopment and in mental illness as explained from a neurobiological perspective in Chapter 4.

In considering the following epidemiological subgroup information, it is important for the reader to know that addiction psychiatry as a field is sensitive to and aware of the harmful effects of adverse sociopolitical–cultural forces, including stigma, racism, misogyny, and anti-LGBTQ-ism on patients. This sensitivity probably comes from the fact that people suffering with both addiction and mental illness are among the most

stigmatized and judged people in the world, and this stigma often must be born (by simple association) not just by these patients, but to a lesser extent by the expert physicians and allied professionals who are dedicated to using science to get them better.

Unfortunately, government-funded efforts and resources used to address addiction in patients as a criminal–legal matter (e.g., in the "war on drugs") have also been admixed with laws and traditions that have reflected systematic racism, and/or disproportionally target the poor who cannot afford good legal representation (or sometimes mental health care). Thus, many of the same legal codes that have attempted to criminalize and punish addictive behavior out of existence also disproportionately target certain racial or socioeconomic groups with government-enforced fines, workhouse stays, and incarceration – all happening in competition with, or to the sacrifice of government funding needed to support evidence-based addiction and mental health care.

Addiction psychiatrists are also aware that stigma, racism, misogyny, anti-LGBTQ-ism, antisemitism, and so on, can operate as a form of group-on-group experiential and emotional trauma that can readily generate or worsen PTSD or affective disorders. Because these mental disorders are also brain conditions that biologically increase addiction risk manifesting as dual-diagnosis disorders (see Chapter 4), addiction psychiatrists are vigilant in trying to help, shield, and recover patients who are suffering in part due to the adverse out-casting and dehumanization effects of stigma, and the other "isms." This vigilance includes the expert capacities of addiction psychiatrists to maintain appropriate nonjudgmental, compassionate therapeutic postures (see Motivational Interviewing in Chapter 5) for all patients, even those who may themselves express highly stigmatizing or bigoted thoughts despite, or because of, their own mental illnesses or internalized trauma histories. Finally, addiction psychiatrists are well familiarized with the necessary work of having to advocate for justice, equity, diversity, and inclusion in medical care and research, because dual-diagnosis patients include people from all racial, ethnic, age, and sexual diversity groups. Moreover, the stigma heaped upon addiction and dual-diagnosis patients in health care, and even from within some sectors of psychiatry, has adversely impacted support for clinical services, professional training, and research, that is greatly needed to more effectively treat patients that addiction psychiatrists take care of.

Mental Illness

The tight epidemiological association and overlap between addiction and mental illness has been a consistent, highly replicated finding across population studies in the US, and throughout the world for many decades. As reviewing this literature is too large for the purposes of this book, we will describe fairly recent US data that is well-representative of the enduring and pervasive scope of the association.

According to NSDUH data from 2018 (SAMSHA, 2019; national sample of n = 7,791 the US population aged 18 or older is estimated to have about 47.6 million people (19.1%) with a mental illness of some kind, with 11.4 million (4.6%) being categorized as have a severe mental illness that is significantly chronic and debilitating. Within each of these groups: 9.2 million (3.7% age 18 or older in US population) have any mental illness and a substance use disorder(s), while 3.2 million (1.3%) have a severe mental illness and a substance use disorder(s). There are three key observations to make about these numbers:

(1) *Addictions and mental illness are closely linked epidemiologically* (i.e., these diseases strike people in highly convergent and overlapping ways in the general population). Considering that 20.3 million of the US population (age 12 and older) has a SUD (non-nicotine) of some kind, these data tell us that about 9.2 million of the 20.3 million with SUDs (equal to 45% of those with SUDs) also have some kind of mental illness. Thus, nearly half of all addictions present in the US are concentrated in only a fifth of the population – those who also have a mental illness.

(2) *Increasing severity of mental illness also corresponds to increasing risk of having an addiction*. Note that while 9.2 million of 47.6 million (or 19%) with any mental illness also have a SUD(s), about 3.2 million of the 11.4 million (or 28%) *with severe mental illness*, have a SUD(s). This means that within the population with any mental illness, 3.2 million of 9.2 million (35%) of the addictions occur in the subpopulation with severe mental illness, even though the severely mental ill make up only 11.4 million/47.6 million = 24% of the population with any mental illness. Thus, people with severe mental illness who make up only 4.6% of the total adult US population, account for 3.2 million/20.3 million or 16% of all SUDs happening in the general adult population. As a rule of thumb then, mental illness roughly doubles the risk of acquiring addiction, whereas severe mental illness nearly quadruples the risk.

(3) These *comorbidity figures, describing the epidemiology of what is variously called dual diagnosis or co-occurring disorders, likely represent* ***underestimates*** *of the close connection between mental illness and addiction*. As mentioned above, these tallies of SUDs *do not include use* and disorders involving tobacco (estimated to be about 21.5% of the population when counting cigarettes, cigars, pipes, dipping, snuff, and chewing), and/or the use of nontobacco nicotine products (vaping, e-cigarettes, nicotine gum). This is a critical omission because we also know that nicotine ranks as among the most addictive and deadly of all addictive drugs, and it is even more concentrated in people with mental illness (>50%) or those with severe mental illness (>75%) than are other addictions.

Taken together, as summarized in Figure 1.1, these numbers make it clear that the overall public health impact of addiction (including its huge associated consequences in generating chronic medical diseases,

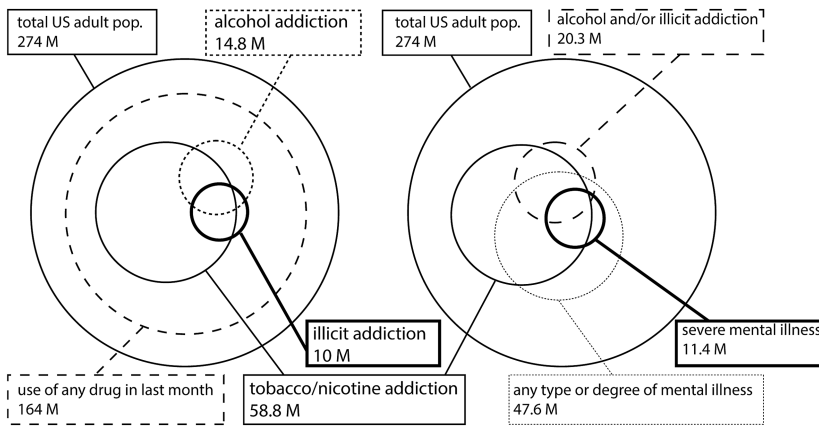

Figure 1.1 2018 US population SUD and mental illness prevalence and comorbidity (based on NSDUH/SAMHSA data). Left panel shows relative scales (size of circles) and overlaps within the US population (12+ years of age) and any substance use (pathological or not) versus addiction spectrum disorders involving tobacco/nicotine, alcohol, and illicit drugs (opioids, marijuana, methamphetamine). Right panel shows relative scales in the US adult population (12+ years of age) and numbers of people with any mental illness/severity versus those with severe mental illness and how those compare and overlap with tobacco/nicotine addictions, and other drug (illicit + alcohol addiction). As per factors described in the text and underreporting due to stigma, rates of substance use and disorders are likely actually greater than depicted here.

injuries, and premature death) is disproportionately and massively shouldered by those who also suffer with mental illness. Although suicide is a major cause of death in people with mental illness, the death toll (and causation of chronic medical diseases and injuries) produced by addictions in the mentally ill is far greater than suicide, even as addiction is also a driver of suicide risk. Chapter 4 will provide an in-depth neuroscientific explanation for the close linkage between mental illness and addiction.

Age: Adolescence to Young and Older Adulthood

Adolescence is the age when most people who go on to acquire addiction, often by their young adult years, begin to experiment with substance use. From the NSDUH data set (the 2018 US sample of $n = 67{,}791$) we can assess the large increases in substance use across these age ranges. These data include past year use that may or may not qualify as representing acquisition of a substance use disorder. In the age range of kids (12–17 years old) to young adulthood (18–25) alcohol use increases about 6.2-fold from 9% of kids to 55.5% of young adults. Cigarette use (not including other forms of tobacco/nicotine) increases about 7-fold from 2.7% to 19.1%. Marijuana use increases about 2.8-fold from 12.5% to 34.8% while misuse of opioids (use of opioids without a prescription) doubles from 2.8% to 5.5%. Notably, heroin use is much smaller than diverted pharmaceuticals in this opioid uptake, going from <0.1% of kids to 0.5% in young adults. Misuse of stimulants (using prescription stimulants that are not prescribed, not including cocaine or methamphetamine) rises 4.3-fold from 1.5% to 6.5%.

Lifespan rates of substance use patterns diagnosable as addictions (based on DSM-5 criteria for substance use disorders involving alcohol, tobacco, cannabis, and opioids) are shown in Table 1.3 (from Vasilenko et al., 2017). These data, drawn from an earlier US representative sample ($n = 36{,}309$; 2012–2013; NESARC-III), as comparable to the 2018 NSDUH data, provide an excellent snapshot of how peri-adolescent experimentation of drugs leads to age and gender-related trajectories of major addictions from 20 to 80 years old. Note how prevalence rates of addictions tend to level off and gradually decline with age after the early 20s, either because the addictions are killing their hosts or these people are able to survive after achieving illness remissions. This kind of pattern has been seen across many studies spanning multiple previous generations and many other countries. It also

holds up well across most major addictive drug types as shown here. Adolescence is thus a rapid period of acquisition of addictions, while adulthood represents a long struggle with the disease, in which there is often only one victor. Chapter 4 provides a neurobiological explanation for adolescent addiction vulnerability that is interestingly similar to and developmentally interactive with mental illness–based addiction vulnerability.

Gender

Males have a higher prevalence of SUDs than females in the US population, also shown in Table 1.3. This trend has generally held up across different addictive drug types, different populations (and nations), and eras of sampling, although the ratios of male to female rates do fluctuate over time. In recent years, some studies have shown that female rates are "catching up" to males with respect to some drugs, suggesting that there are strong environmental–cultural forces in play that modify this risk, just as much as there are biological–genetic risk factors and behavioral traits associated with being male that increase addiction risk compared to females. Notably, although most studies have shown much greater risk of acquiring addiction in men compared to women, there is also evidence that when women do get it, it happens with a faster rate of onset. This effect, called **telescoping**, refers to a shortened amount of time from first use of a drug to onset of addiction, which may reflect situations where an individual has an unusually high concentration of risk factors for addiction (e.g., presence of mental illness) that may counteract relatively protective factors (e.g., being female). The data collection in Table 1.3, like nearly all large-scale studies, does not include analysis of people defined by additional gender/sex/sexual orientation classifications, such as the transgender population. There is less information available about nonbinary populations, and transgender data are often included within the umbrella of LGBTQ rather than on their own.

LGBTQ Populations

The LGBTQ population has more than twice the rates of using addictive substances compared to people who identify themselves as being in the cis-gendered heterosexual category. This is seen with alcohol binge

Table 1.3 Age and gender-based prevalence rates for substance use disorders

	Alcohol	%	Tobacco	%	Cannabis	%	Opioid	%
Age	Male	Female	Male	Female	Male	Female	Male	Female
20	29	23	22	16	14	7	3	3
30	30	17	30	21	5	3	3	2
40	19	11	26	19	3	2	2	2
50	15	10	26	20	3	2	3	2
60	11	5	21	15	2	1	1	1
70	6	2	10	7	1	1	1	<1
80	2	1	5	5	<1	<1	<1	<1

National Epidemiologic Survey of Alcohol and Related Conditions (NESARC-III); n = 36,309 participants.
Based on DSM-5 criteria for substance use disorders/addictions (% of age cross-section). Percentages are bounded by 95% confidence intervals of approximately ±1% (Vasilenko et al., 2017).

drinking, marijuana use, and prescription pill use. Per NIDA data, LBGTQ individuals may start using addictive substances at earlier ages and thus eventually enter treatment with higher levels of addiction disease severity. Mental illness, which generates addiction vulnerability as discussed above, also occurs at higher rates in the LGBTQ community, as a possible consequence of trauma-related brain responses to social persecution and out-casting. Much more research is needed to understand the causality, neurobiology, and unique treatment needs of the LGBTQ community with addictions and dual-diagnosis disorders.

Racial/Ethnic Groups

Susceptibility to addiction disorders is comparable across most racial-ethnic populations. Higher- or lower-than-average rates of certain types of SUDs in certain ethnic groups are often associated with cultural or socioeconomic factors that are discussed in the remainder of this chapter. However, Chapter 4 will mention some genetic differences in addiction risk that do occur in different frequencies across different ethnic-racial groups. Regardless, a higher prevalence of addiction in any specific subpopulation can lead to downward socioeconomic drift, with transgenerational transmission of disease risk, making it even more difficult for family lines within certain subpopulations to recover.

Education

Lower levels of education have been found in some studies to be correlated with higher rates of substance misuse or addiction. However, this association is complex. A number of premorbid risk factors (presence of mental illness, family instability) that can increase addiction risk later on can also cause derailment of educational attainment. So can the onset of heavy substance use during teenage years. Per 2010 NSDUH data, those without a high school degree had a higher rate (10.2%) of SUDs than those with a high school degree (8.5%), followed by adults who finished college having the lowest rates (6.3%). However, the highest rate was seen in adults with some college education who did not finish their degree (10.6%). It is important to note that addiction is not a sign of lower intelligence. The book *Deaths of Despair and the Future of Capitalism* (Case and Deaton, 2020) outlines how college education confers more

than just a degree but grants social access to higher-paying careers, or careers that do not require physical exertion or introduce as much risk of injuries (e.g., that may lead to chronic opioid prescriptions), or allow for better health insurance plans. Having a college degree is generally associated with lower mortality rates due to suicide and drug overdose. It also associates with lower risk of alcoholic liver disease, lower pain scores, higher rates of marriage, and higher self-assessed overall health scores.

Interpretation of these associations should be made with caution, as there are likely many causal dynamics (some of which are hard to capture in studies) that could be giving rise to this association. Clearly, there are examples where an inverse relationship between lower addiction risk and higher educational obtainment (or socioeconomic status) does not hold up as demonstrated by the notable exception of physicians. Although doctors are among the most highly educated, health aware, and well-paid members of society, they suffer with addictions at rates that are comparable to or even higher than the general population (e.g., especially in the fields of anesthesiology, emergency medicine, and orthopedic surgery). Job-associated environmental factors like long work hours, high stress, and easy access or exposure to controlled drugs while on the job are associated with this increased risk. Notably, however, physicians as a group also show rates of successful addiction treatment outcomes that are better than the general population. This may be due in part to physicians enjoying better access to (and being able to afford) better-than-average quality and durations of care. A long-range goal of addiction psychiatry is to eliminate such disparities in access to care for all people regardless of socioeconomic status.

Another well-known occupational sector that suffers relatively high levels of addiction morbidity and mortality is in the upper echelons of the entertainment industry. Despite often being widely recognized for having rare intellectual gifts of creativity and high earnings, movie stars and rock stars are known to suffer higher risk of addictions and lethal outcomes. Multiple personal and occupational factors are likely in play to drive this risk, one of which may be the psychiatrically toxic effects of extreme fame. Extreme wealth may also, quite ironically, put entertainment stars at risk, because it may increase the risk of becoming surrounded by people (or pseudo-professionals) who want to use them for their fame and money rather than take care of them.

Employment Status

As already suggested in the section on the economic impacts of addiction, lower employment status is correlated with higher rates of substance misuse and addiction. As per NSDUH (2010) data, unemployed adults showed the highest rates of SUDs (17.5%) followed by adults employed part-time (11.2%) and adults employed full-time (8.4%). Educational attainment, family employment, and family socioeconomic status are all intercorrelated variables in the US, which are also tied to access to quality health care. Given that addictions cause damage to educational attainment and occupational performance, we observe that unemployment, low education, and addiction are all linked through multiple bidirectional relationships. For example, although substance use can impair job performance, unemployment can represent a significant source of psychological stress and mental health problems, which can raise addiction vulnerability. In turn, both mental illness and addiction increase risk of job loss and loss of insurance coverage (which in the US is tightly linked with employment) needed to support access to mental health and/or addiction treatment. As already mentioned, these trends should not lead to the assumption that addicted patients are generally poor and/or unemployed. Indeed, about two-thirds of people with treatable active SUDs are gainfully employed full-time. Regardless, an important take home implication of the fact that addiction and comorbid mental illness can produce downward educational and socioeconomic drift is that effective treatment has the potential to stop or even reverse this drift for patients and their families. Thus, the practice of addiction psychiatry offers society a positive social and economic impact beyond its direct public health benefits, in preventing worsening socioeconomic divisions.

Criminal Justice System Population

Adults who had been on parole or released from jail in the past year have 3–8 times greater rates SUDs (depending on specific drug type) comparable to a general population sample (NSDUH data collected 2002–2014, described in Fearn et al., 2016). Nicotine addiction is also estimated to range from 50% to 90% (three- to six-fold general population rates) in Americans with criminal justice involvement both before and after incarceration. Similarly increased rates of mental illness are also found in

incarcerated populations (e.g., as large city jails have replaced psychiatric treatment centers). Unfortunately, in the **post deinstitutionalization era** (c. 1960–2000) when most long-term psychiatric hospital beds were eliminated, and with the advent of "the war on drugs," large numbers of people that have or are susceptible to mental illness, addictions, and dual-diagnosis disorders have been sequestered away from access to evidence-based treatment into circumstances of homelessness, criminalization, and mass incarceration. This dynamic, happening with substantial force over the last half century in the US and much of the western world, was initially described by the British psychiatrist Penrose over 80 years ago. In **the Penrose effect**, there tends to be (across modern economies) a reciprocal-inverse relationship between prison populations and psychiatric treatment infrastructures. Because mental illness is a strong biological vulnerability condition for addiction (as we describe in detail in Chapter 4), the "war on drugs," has essentially and unfortunately operated as an accelerant for the Penrose effect (Grecco and Chambers, 2019). This dynamic has in turn resulted in the overidentification of criminality with mental illness and addiction. This effect not only compounds stigma against these disorders, but it concretely damages society's (and healthcare systems') emphasis on and financial support for treatment. While the cost of mass incarceration is in competition with the costs of providing higher education and providing mental health care, patients who are criminalized often lose health insurance directly as a consequence of incarceration, or they are rendered unemployable (and thus uninsured) due to criminal records that are drug-use related.

Certainly, there remains a vital role for the legal system and law enforcement in monitoring, regulating, controlling, and interdicting the production, distribution, and misapplication of additive-psychoactive compounds. This is especially needed for stopping distribution by illegal channels and large-scale distribution networks mediated by organized crime groups, foreign adversaries, or even doctors and clinics that are operating as drug dealers under the disguise of health care. However, an overemphasis on prosecuting and incarcerating low-level consumers of addictive drugs in the war on drugs has had the unintended consequence of contributed to a weakening of treatment infrastructure, professional training, workforce development, and insurance coverage for behavioral health that is needed to prevent and treat addiction more

effectively. Past and ongoing failures of the US healthcare system and its mental health sectors to fully accept addiction as a biomedical condition, and to grasp and respond to the interconnection between mental illness and addiction, has represented a root cause of the US iatrogenic opioid epidemic. Beginning in the 1990s and still unabated, the addiction epidemic in the US has grown in parallel with the mass incarceration of mentally ill/addicted people and an increasing death toll due to addictions and overdoses in this very same population.

HIV/AIDS

About a third to half of individuals with human immunodeficiency virus (HIV) are estimated to have had an SUD diagnosis, often involving multiple drugs. The two primary routes of contracting HIV – via unprotected sex or using unsterile needles – are both associated with substance use. Several forms of mental illness and substance use (e.g., involving opioids, methamphetamine, and alcohol) produce or are associated with high levels of impulsivity and/or rapid progression through multiple sexual partners. All these behaviors increase the risk of acquiring HIV and addictions. HIV and addiction are so often intertwined that an outbreak of one can be a sign for the other, as happened in the HIV outbreak in Scott County, Indiana in 2015. This event represented one of the largest and most explosive HIV outbreaks in US history. The rural town of Austin in Scott County, home to a population of 2,000 people, encompassed a remarkably high rate (25% of the total population!) who were not just opioid-addicted, but were actively injecting diverted pharmaceutical opioids (predominantly oxymorphone) that required delivery through large-bore needles. Among these 500 intravenous drug users, over 200 cases of HIV had spread in just 6 months.

In Austin, the makings of a perfect storm had emerged in a rural area, at the height of the iatrogenic opioid epidemic, where there was little to no access to legitimate addiction treatment, and the main approach to dealing with addiction had been arresting and jailing people. Generally, any group of people engaging in active iv. drug use who are HIV positive, and are unable to access addiction treatment, can show a high rate of HIV transmission. This occurs for several reasons, including the fact that

patients in active addiction tend to be less likely to have their HIV diagnosed or be compliant on antiviral medications while maintaining other high-risk behaviors. Ironically, although the epidemic of addiction that led to the Austin HIV outbreak generated a quite rapid and effective state and federal response focused on the HIV (by 2016 the HIV spread had essentially been stopped, and no one had died of AIDS), the county had suffered for many years with incredibly high rates of per-capita incarcerations and overdose deaths. These trends continued due to the underlying addiction that was never adequately recognized or addressed as a disease in its own right. The failure of government and affiliated healthcare entities to have properly recognized and addressed the underlying addiction disease that caused the HIV outbreak, on par with how the HIV itself was decisively addressed, was a clear and stunning illustration of the effects of stigma, disparities in health equity, and **lack of parity**. Lack of parity refers to failures of healthcare systems and insurance companies to support adequate services needed for the diagnosis and treatment of addiction and dual-diagnosis diseases on par with other diseases that addiction may lead to, like HIV.

Location and Era

Different regions of a country can show differential rates of addiction, and addiction-related health consequences. In the United States, SUDs (excluding nicotine) have been reported to vary from highest to lowest rates regionally as follows: West (10%), Northeast (9.4%), Midwest (8.2%), South (7.8%). However, specific substances may not follow the same overall trends because geographical differences can be highly drug-specific based on the conditions of local supply or knowledge of drug-making. For example, methamphetamine use has been most prevalent in the West, Midwest, and South, with much lower levels of use in the Northeast. These patterns have reflected both the manufacturing techniques involved in Meth production (which readily utilize rural–agricultural products) and black-market importation trade routes. In the meantime, although the iatrogenic opioid epidemic started out strong particularly in rural, predominantly poor, white regions of the Midwest and Appalachia, it has evolved to attack more urban nonwhite populations as well in recent years. Strikingly, geographical proximity and access to primary care and pharmacies in the Midwest has been

identified as a risk factor acquiring opioid addiction, as a reflection of its iatrogenic causality.

The spread of street knowledge that propagated the easy manufacturing of crack cocaine (smokable free base) from the powder form of cocaine (which is consumed by snorting) led to a significant epidemic of crack cocaine addiction in the 1990s that was far larger and more detrimental than patterns of cocaine use in the 1970s and 1980s. This epidemic, predominantly hitting large urban centers, especially in the Northeast, involved an interesting interplay between gang-controlled trade routes for the drug and knowledge that cocaine, in its smoked (crack) form, is a far more addictive. A parallel dynamic occurring in the legal tobacco industry has involved deliberate changes to the design and chemical content of cigarettes (e.g., including adding menthol) by tobacco companies to increase the addiction potency of their products (the reader is encouraged to see 1999 film *The Insider*, which dramatizes part of this history).

The Big Picture View of Addiction Psychiatry in Preventative and Public Health

This chapter has begun to describe the central role addiction disease plays as a major public health threat that is a leading root cause of body injuries, general medical illness, and all-cause mortality. At the same time, addiction is closely, causally interlinked with mental illness on the levels of whole populations and within individual's brains (as we explore in Chapter 4). Accordingly, addiction psychiatry stands as a field of medicine (and form of training) that uniquely equips doctors to prevent and stop this complex disease propagation as it spreads from mental illness to addiction (and back again), eventually leading to very serious body organ damages, injuries, infections, and premature death. As a specialty that recognizes, embraces, and tackles complex comorbidities in behavioral health, addiction psychiatry is adept at interdicting dual-diagnosis disease impact as it tends to flow not just between brain and body organs, but transgenerationally within families (Figure 1.2), and from the suffering individual to our suffering society. In the next chapters we describe how addiction psychiatrists understand addiction disease clinically and neurobiologically, and how we diagnose it and treat it based on this knowledge. These descriptions are intended not just to educate the next generations of doctors and scientists who will

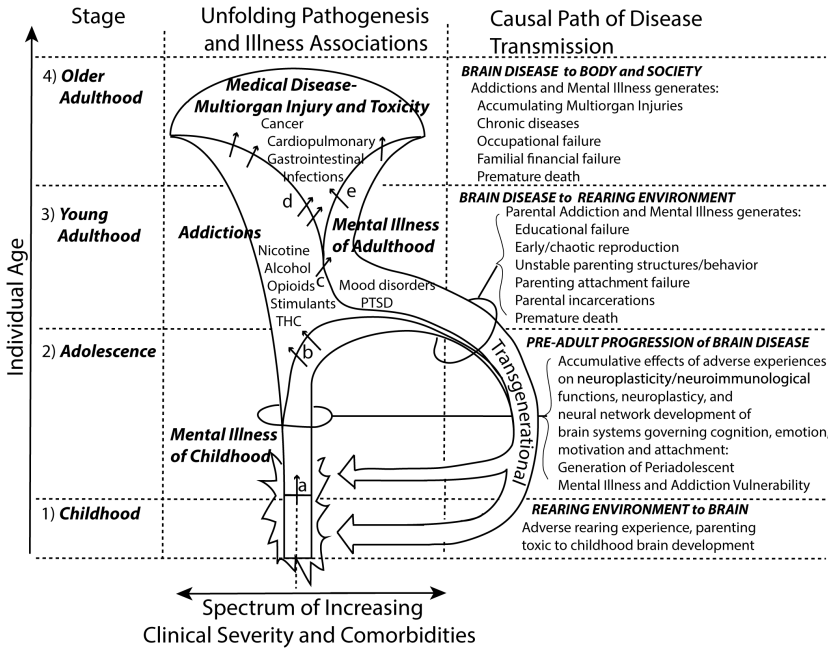

Figure 1.2 "Bugle-horn comorbidity pathway" of mental illness, addiction, and medical (multiorgan) morbidity. In (1) childhood and (2) adolescence, adverse rearing environments, impaired parental behavior, and attachment failures are biologically neurotoxic to the developing brain (and may compound with genetic loading for mental illness) resulting in preclinical or emerging signs of mental illness (a, arrow). In turn, mental illness–induced neurobiological vulnerability to drug addiction leads to the onset of one or more addictions in adolescence and/or (3) young adulthood (b, arrows), which further exacerbates the neurobiological and clinical dimensions of the underlying mental illness (c, arrow). The mental illness/addiction comorbidity experienced during young adulthood results in chaotic reproduction and parenting impairments and instability, exposing offspring to a new cycle of adverse rearing environments and experiences. The later causal dynamic (handle of the bugle) represents both a transgenerational and transenvironmental–neurobiological cycle: the brain illness of the parent generates an adverse environment for the child; the adverse environment for the child conspires with their genetic inheritance to generate adult mental illness, addiction, and impairments in their parenting capabilities for the next generation, and so on. Into (4) older adulthood, the scope, severity, and impact of addictions and mental illness comorbidities worsen (the girth of the bugle enlarges) so that greater varieties and severity of multiorgan toxicities and injuries (i.e., chronic medical diseases and early death rates) and social damages (financial collapse, criminalization) accumulate as consequences of addiction disease (d, arrows) and mental illness (e, arrows). (Permission granted for reproduction by Taylor and Francis; see Zarse, 2019, Chapter 4.)

have to confront this remarkable and terrible disease of the brain, but to generate larger interest and collective efforts in growing addiction psychiatry to where it becomes a major cornerstone of both behavioral health and public health.

BIBLIOGRAPHY

Arnaudo, C. L., B. Andraka-Christou, and K. Allgood. 2017. Psychiatric co-morbidities in pregnant women with opioid use disorders: Prevalence, impact, and implications for treatment. *Curr Addict Rep*, 4: 1–13.

Case, A., and A. Deaton. 2020. *Deaths of Despair and the Future of Capitalism*. Princeton, NJ: Princeton University Press.

Chambers, R. A. 2013. The addiction psychiatrist as dual diagnosis physician: A profession in great need and greatly needed. *J Dual Diagn*, 9: 260–66.

Chambers, R. A., and M. N. Potenza. 2003. Neurodevelopment, impulsivity, and adolescent gambling. *J Gambl Stud*, 19: 53–84.

Chou, S. P., R. B. Goldstein, S. M. Smith, B. Huang, W. J. Ruan, H. Zhang, J. Jung, T. D. Saha, R. P. Pickering, and B. F. Grant. 2016. The epidemiology of DSM-5 nicotine use disorder: Results from the National Epidemiologic Survey on Alcohol and Related Conditions-III. *J Clin Psychiatry*, 77: 1404–12.

Compton, W. M., Y. F. Thomas, F. S. Stinson, and B. F. Grant. 2007. Prevalence, correlates, disability, and comorbidity of DSM-IV drug abuse and dependence in the United States: Results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Arch Gen Psychiatry*, 64: 566–76.

Els, C. 2007. Addiction is a mental disorder, best managed in a (public) mental health setting – But our system is failing us. *Can J Psychiatry*, 52: 167–69, discussion 174.

Esang, M., and S. Ahmed. 2018. A closer look at substance use and suicide. *Am J Psychiatry Resid J*, 13: 2–12.

Fearn, N. E., M. G. Vaughn, E. J. Nelson, C. P. Salas-Wright, M. DeLisi, and Z. Qian. 2016. Trends and correlates of substance use disorders among probationers and parolees in the United States 2002–2014. *Drug Alcohol Depend*, 167: 128–39.

Fuhrmann-Berger, J. 2018. The economic impact of opioid addiction. *Strategic HR Rev*, 17: 198–203.

Gonzales, K., J. Roeber, D. Kanny, A. Tran, C. Saiki, H. Johnson, K. Yeoman, T. Safranek, K. Creppage, A. Lepp, T. Miller, N. Tarkhashvili, K. E. Lynch, J. R. Watson, D. Henderson, M. Christenson, S. D. Geiger, Control Centers for Disease, and Prevention. 2014. Alcohol-attributable deaths and years of potential life lost – 11 States, 2006–2010. *MMWR Morb Mortal Wkly Rep*, 63: 213–16.

Grant, B. F., D. S. Hasin, S. P. Chou, F. S. Stinson, and D. A. Dawson. 2004. Nicotine dependence and psychiatric disorders in the United States: Results from the

National Epidemiologic Survey on alcohol and related conditions. *Arch Gen Psychiatry*, 61: 1107–15.

Grant, B. F., T. D. Saha, W. J. Ruan, R. B. Goldstein, S. P. Chou, J. Jung, H. Zhang, S. M. Smith, R. P. Pickering, B. Huang, and D. S. Hasin. 2016. Epidemiology of DSM-5 drug use disorder: Results from the National Epidemiologic Survey on Alcohol and Related Conditions-III. *JAMA Psychiatry*, 73: 39–47.

Grecco, G. G., and R. Andrew Chambers. 2019. The Penrose effect and its acceleration by the war on drugs: A crisis of untranslated neuroscience and untreated addiction and mental illness. *Transl Psychiatry*, 9: 320.

Hartzler, B., J. C. Dombrowski, H. M. Crane, J. J. Eron, E. H. Geng, W. Christopher Mathews, K. H. Mayer, R. D. Moore, M. J. Mugavero, S. Napravnik, B. Rodriguez, and D. M. Donovan. 2017. Prevalence and predictors of substance use disorders among HIV care enrollees in the United States. *AIDS Behav*, 21: 1138–48.

Hedegaard, H., A. M. Minino, M. R. Spencer, and M. Warner. 2021. *Drug Overdose Deaths in the United States, 1999–2020*. NCHS Data Brief no. 248: 1–8. Hyattsville, MD: National Center for Health Statistics.

Heron, M. 2018. Deaths: Leading causes for 2016. *Natl Vital Stat Rep*, 67: 1–77.

Hughes, J. R., D. K. Hatsukami, J. E. Mitchell, and L. A. Dahlgren. 1986. Prevalence of smoking among psychiatric outpatients. *Am J Psychiatry*, 143: 993–97.

Ives, K., B. Christiansen, M. Nolan, J. T. Kaye, and M. C. Fiore. 2022. Nine years of smoking data from incarcerated men: A call to action for tobacco dependence interventions. *Prev Med Rep*, 29: 101921.

Kessler, R. C. 2004. The epidemiology of dual diagnosis. *Biol Psychiatry*, 56: 730–37.

Kranzler, H. R., and R. N. Rosenthal. 2003. Dual diagnosis: Alcoholism and co-morbid psychiatric disorders. *Am J Addict*, 12(Suppl 1): S26–40.

Krueger, A. B. 2017. Where have all the workers gone? An inquiry into the decline of the U.S. labor force participation rate. *Brookings Pap Econ Act*, 2017(2): 1–87.

Labouvie, E. 1996. Maturing out of substance use: Selection and self-correction. *J Drug Issues*, 26: 457–76.

Lasser, K., J. W. Boyd, S. Woolhandler, D. U. Heimmerlstein, D. McCormick, and D. H. Bor. 2000. Smoking in mental illness: A population-based prevalence study. *JAMA*, 284: 2606–10.

Macy, B. 2018. *Dopesick: Dealers, Doctors, and the Drug Company that Addicted America*. New York, NY: Little, Brown & Co.

Mateu-Gelabert, P., and H. Guarino. 2018. The opioid epidemic and injection drug use: MIPIE and health harms related to the injection of prescription opioids. *Int J Drug Policy*, 57: 130–32.

McCabe, S. E., B. T. West, T. L. Hughes, and C. J. Boyd. 2013. Sexual orientation and substance abuse treatment utilization in the United States: Results from a national survey. *J Subst Abuse Treat*, 44: 4–12.

McLellan, A. T., D. C. Lewis, C. P. O'Brien, and H. D. Kleber. 2000. Drug dependence, a chronic medical illness: Implications for treatment, insurance, and outcomes evaluation. *JAMA*, 284: 1689–95.

Mokdad, A. H., J. S. Marks, J. S. Stroup, and J. L. Gerberding. 2004. Actual causes of death in the United States, 2000. *JAMA*, 291: 1238–45.

National Center for Statistics and Analysis. 2015. *2014 Crash Data Key Findings* (Traffic Safety Facts Crash Stats. Reports No. DOT HS812219). Washington, DC: National Highway Traffic Safety Administration.

National Safety Council. 2021. *Preventable Deaths Odds of Dying*. Itasca, IL: National Safety Council.

Nelson, D. E., D. W. Jarman, J. Rehm, T. K. Greenfield, G. Rey, W. C. Kerr, P. Miller, K. D. Shield, Y. Ye, and T. S. Naimi. 2013. Alcohol-attributable cancer deaths and years of potential life lost in the United States. *Am J Public Health*, 103: 641–48.

NIDA. 2023a. *Drug Overdose Death Rates*. Bethesda, MD: National Institute on Drug Abuse.

NIDA. 2023b. *Substance Use and SUDs in LGBTQ* Populations*. Bethesda, MD: National Institute on Drug Abuse.

Oreskovich, M. R., T. Shanafelt, L. N. Dyrbye, L. Tan, W. Sotile, D. Satele, C. P. West, J. Sloan, and S. Boone. 2015. The prevalence of substance use disorders in American physicians. *Am J Addict*, 24: 30–38.

Penrose, L S. 1939. Mental disease and crime: Outline of a comparative study of European statistics. *Br J Med Psychol*, 18: 1–15.

Pompili, M., G. Serafini, M. Innamorati, G. Dominici, S. Ferracuti, G. D. Kotzalidis, G. Serra, P. Girardi, L. Janiri, R. Tatarelli, L. Sher, and D. Lester. 2010. Suicidal behavior and alcohol abuse. *Int J Environ Res Public Health*, 7: 1392–431.

Regier, D. A., M. E. Farmer, D. S. Rae, B. Z. Locke, S. J. Keith, L. L. Judd, and F. K. Goodwin. 1990. Comorbidity of mental disorders with alcohol and other drugs of abuse. *JAMA*, 264: 2511–18.

Salmond, S., and V. Allread. 2019. A population health approach to America's opioid epidemic. *Orthop Nurs*, 38: 95–108.

SAMSHA. 2012. *Results from the 2010 National Survey on Drug Use and Health: Mental Health Findings*. NSDUH Series H-42, HHS Publication No. (SMA) 11–4667. Rockville, MD: Substance Abuse and Mental Health Services Administration.

SAMSHA. 2019. *Key Substance Use and Mental Health Indicators in the United States: Results from the 2018 National Survey on Drug Use and Health*. NSDUH Series H-54, HHS Publication No. PEP19-5068. Rockville, MD: Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality.

Strain, E. C., R. K. Brooner, and G. E. Bigelow. 1991. Clustering of multiple substance use and psychiatric diagnoses in opiate addicts. *Drug Alcohol Depend*, 27: 127–34.

Trull, T. J., K. J. Sher, C. Minks-Brown, J. Durbin, and R. Burr. 2000. Borderline personality disorder and substance use disorders: A review and integration. *Clin Psychol Rev*, 20: 235–53.

US Department of Health and Human Services. 2014. *The Health Consequences of Smoking: 50 Years of Progress. A Report of the Surgeon General*. Atlanta, GA: US Department of Health and Human Services, Centers for Diseases Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office of Smoking and Health.

Vasilenko, S. A., R. J. Evans-Polce, and S. T. Lanza. 2017. Age trends in rates of substance use disorders across ages 18–90: Differences by gender and race/ethnicity. *Drug Alcohol Depend*, 180: 260–64.

Warner, L. A., R. C. Kessler, M. Hughes, J. C. Anthony, and C. B. Nelson. 1995. Prevalence and correlates of drug use and dependence in the United States: Results from the NCS. *Arch Gen Psychiatry*, 52: 313–21.

Weinberger, A. H., M. Gbedemah, M. M. Wall, D. S. Hasin, M. J. Zvolensky, and R. D. Goodwin. 2018. Cigarette use is increasing among people with illicit substance use disorders in the United States, 2002–14: Emerging disparities in vulnerable populations. *Addiction*, 113: 719–28.

Winkelman, T. N. A., L. K. Admon, L. Jennings, N. D. Shippee, C. R. Richardson, and G. Bart. 2018. Evaluation of amphetamine-related hospitalizations and associated clinical outcomes and costs in the United States. *JAMA Network Open*, 1: e183758-e58.

Winkelman, T. N. A., K. Diaz Vickery, and A. M. Busch. 2019. Tobacco use among non-elderly adults with and without criminal justice involvement in the past year: United States, 2008–2016. *Addict Sci Clin Pract*, 14: 2.

Woolf, S. H., and H. Schoomaker. 2019. Life expectancy and mortality rates in the United States, 1959–2017. *JAMA*, 322: 1996–2016.

Wright, E. R., H. E. Kooreman, M. S. Greene, R. A. Chambers, A. Banerjee, and J. Wilson. 2014. The iatrogenic epidemic of prescription drug abuse: County-level determinants of opioid availability and abuse. *Drug Alcohol Depend*, 138: 209–15.

2

Specific Symptom Sets: Clinical Phenomenology

Learning Points

- **Intoxication and withdrawal are acute/transient syndromes generated by highly dynamic interactions between different substances and specific brain substrates.** For a given drug type, intoxication and withdrawal are largely opposite symptom sets. The severity, quality, and dangerousness of intoxication and withdrawal varies by type of substance, route of drug intake, and the individual's history of use.
- **Tolerance develops with chronic substance use resulting in a decreasing intensity of intoxication with repeated use.** This effect is neurobiologically connected with an increasing severity of withdrawal symptoms when the drug use is abruptly halted.
- **Addiction is a progressive disease of motivational control that is neurobiologically, behaviorally, and temporally distinct from intoxication, withdrawal, and tolerance**. Addiction involves pathological growth (i.e., sensitization) of motivations and behaviors devoted toward the continuation of drug acquisition and use.
- **There are many widely held myths for explaining substance use disorders that are scientifically unsupported, may worsen**

stigma, and ultimately distract from understanding addiction as a biomedical disease process. These myths variously try to explain chronic substance use as judgment narratives about the "good" or "bad" intentions or "logic" of use pertaining to the effects of intoxication and/or withdrawal (e.g., mentally ill people are justifiably "self-medicating"; substance users are "bad people"). However, addiction is a progressive disease of motivation involving a malfunctioning of cognition, decision-making, and free will that is normally driven by healthy motivation. There is no rationale or logic to addiction, any more than there is to other diseases like cancer; there is no fundamental connection between addiction and drug-specific intoxication/withdrawal syndromes.

- **Different addictive drug types produce different acute intoxication/withdrawal profiles through different psychobiological mechanisms, but they produce similar chronic reinforcing effects through shared neurocircuits that control motivation.** This thematically similar pharmacological activity in brain pathways that control behavioral reinforcement and sculpt motivational behavioral repertoires allows different addictive drugs to produce similar clinical addiction syndromes. In contrast, their diverse intoxication profiles are governed by a much more anatomically diverse psychopharmacology, allowing their "highs" to be quite different and sometimes opposite from one another.
- **Drug liking $\neq$ drug wanting.** Liking the high (intoxication) that a drug produces has little to do with the wanting for the drug (compulsive urges and craving) a person experiences in advanced addiction.

Introduction

Key Terms and Concepts

Toward reaching a deeper understanding about what addiction is, we will first define and clarify common terms used to label it or its key aspects. Then we will discuss what addiction is not, or what it is often misunderstood as being, in a *myth-busters* section. There are four key

terms that describe a spectrum of brain syndromes that all fall under the larger umbrella term of **substance use disorders (SUDs)**:

1. Intoxication
2. Withdrawal
3. Tolerance
4. Addiction

Consider how these four terms may or may not be related to each other as illustrated by the following questions:

- Does a person need to be intoxicated to be addicted?
- Does a person need to be addicted to experience withdrawal?
- Would a person need to first be intoxicated to have withdrawal?
- Would treating withdrawal treat addiction?
- Is a person with tolerance to a drug addicted to that drug?

In fact, one of the above four terms belongs in a different category from the others, whereas the other three are quite interrelated. Which term do you think is the outlier and why? A major point of this chapter is to clearly answer this question. As the reader may guess, *addiction* is the outlier term. As a lead up to a better understanding of what addiction is, we will start by defining the other terms first.

Intoxication and Withdrawal

Intoxication and withdrawal are the yin and yang of the acute psychoactive effects of substance use. Intoxication is a time-limited state during which an individual is under the *initial* effects of a substance, predominantly as the drug is on the way in (i.e., as drug levels are rising in the brain). In contrast, withdrawal happens when the drug is on the way out (i.e., declining or recently eliminated). To understand the link between intoxication and withdrawal, start with the simple, yet not always obvious, revelation that *every intoxication is followed by a withdrawal*. The effects of withdrawal are largely opposite to those of intoxication.

Medical students spend a great deal of time learning how human bodies are resilient to environmental stresses and change thanks to the many built-in mechanisms that maintain biological **homeostasis**. For

example, take one of our vital signs – the maintenance of body temperature at around 98.6°F (37°C). The body works constantly to keep this optimal operating temperature stable, despite the ever-changing external temperature. When you sweat in the summer, that is your body's attempt to cool off. When you shiver in winter and feel goosebumps, that is an attempt to create and conserve heat.

The brain also implements many elegant and sophisticated physiologic mechanisms that strive for homeostasis in the face of environmental input and stimuli. The brain's first line of defense against psychoactive molecules (which by definition create some kind of action and/or instability in the brain) is, of course, the **blood brain barrier (BBB)**. All drugs that are psychoactive and addictive are able to breach the BBB. Most people reading this book have consciously invited one of society's most frequently used addictive drugs, alcohol, to breach their BBB, to experience its intoxicating effects. So let's use this drug as a prime, vivid, and widely experienced example to explain intoxication and withdrawal.

Alcohol Intoxication and Withdrawal

The neurotransmitter **GABA (gamma-aminobutyric acid)**, which (unsurprisingly) acts on GABA receptors, occurs naturally in the brain as a key ***inhibitory*** **neurotransmitter**. As such, GABA's release onto GABA receptors on the postsynaptic membrane of neurons (which receive GABA signaling from other neurons) results in *decreased* neuronal excitability (electrical signaling activity) at the receiving neuron. Now, when a person drinks alcohol, it readily gets into the brain and produces a significant effect at those same GABA receptors, everywhere they exist all over the brain. Keep in mind that alcohol (also known as ethanol, or **ETOH**) is a very simple solvent molecule that is actually quite neurobiologically "dirty"; that is, it has many complex neurotransmitter effects beyond its ability to activate the GABA (A) subtype inhibitory receptors, including having effects on the brain's key excitatory neurotransmitter system that is mediated by **glutamate**. However, alcohol's GABAergic effect, which slows down the overall activity of the postsynaptic neuron, is predominant, and more so with higher doses. During heavy alcohol intoxication, this **GABA agonism** results in decreased activity in many (but not all) neural networks of the brain. We say many, but not all, because of course, some GABA receptors

are on GABAergic neurons, so alcohol can actually work to inhibit inhibitory circuits (often termed **disinhibition**). This produces a net *hyperactivation* at the end point of some neural communication pathways (e.g., where GABA neurons are in series). Thus, the net effect of alcohol is to produce both a decrement and a disorganization of overall brain network activity. This helps to explain the notable effects of severe alcohol intoxication: muscle relaxation, slurred speech, disinhibited behavior and emotion, unsteady gait, decreased anxiety, decreased nociception, lower cardiovascular vital signs, and sedation/somnolence. The alcohol-intoxicated individual is experiencing the effects of alcohol causing their neurons to not fire as effectively. Yet, with homeostasis, which occurs even in the early stages of intoxication, the brain is rapidly and constantly working hard to reverse these neurotransmission/reception imbalances (and clinical symptoms) caused by the alcohol. Why? Because being drunk, or in any kind of acute dysregulated state of global central nervous system (CNS) dysfunction (i.e., delirium, of which severe alcohol intoxication is one example) can be very dangerous for the individual. So, the brain is always trying not to be in a state of delirium (regardless of the cause) because it can readily be lethal!

Now consider alcohol withdrawal, which, by the way, is the most dangerous withdrawal state of all the addictive substances. In moderate alcohol withdrawal a person experiences muscle tremors, agitation, headache, increased anxiety, insomnia, general **sympathetic nervous system activation** including heart rate and blood pressure increases, and so on. In more severe cases, a person can experience potentially fatal seizures, hallucinations, excited delirium (including hallucinations and delusions), arrhythmias with severe hypertension and imminently lethal cardiovascular crisis (often identified as **delirium tremens** or **DTs**).

Notice how most of the symptoms of alcohol withdrawal are opposite to those of intoxication. For example, compare muscle relaxation versus stiffness/tremors, decreased anxiety versus increased anxiety, or sedation versus insomnia. To understand how withdrawal is biophysically linked with intoxication, *via homeostasis*, let's consider how homeostasis is working during intoxication in the lead up to withdrawal. During alcohol intoxication, the brain makes various rapid "real-time" adjustments, such as decreasing the level of GABA released presynaptically and/or decreasing the number of GABA receptors activated postsynaptically to compensate for the lower-than-normal electrical activity in many regions of the brain that

are regulated by "GABAergic tone." These adjustments have the effect of returning electrical activity (i.e., **action potential generation and propagation** across neuronal axons) and neurotransmission (predominantly of glutamate signaling) back upwards, closer to normal baseline levels despite the presence of alcohol. This is great and amazing, and certainly keeps the severity of intoxication restrained (and more so if the person is not drinking too much, too quickly, giving homeostasis time to work). But there is a problem with all this: brain homeostatic mechanisms that are counteracting the effects of alcohol intoxication are acting independently from, and not in much correlation with, body mechanisms (largely in the liver) that are simultaneously working to decrease and eliminate the alcohol from the body and brain. So now, as the alcohol is being massively metabolized and eliminated from the brain and blood stream (at a rate that exceeds consumption, or after consumption has ended), the brain's homeostatic efforts become increasingly *unopposed* by alcohol, which results in a state of overcorrection. This is withdrawal. In the case of alcohol, this overcorrection causes increased electrical activity in many regions of the brain (which generate the signs and symptoms of alcohol withdrawal). But of course, over time, even this overcorrection dissipates (or is itself corrected), as the sustained absence of alcohol allows affected brain regions to return to their baseline receptor activity levels, thus ending withdrawal.

With this homeostatic framework of intoxication–withdrawal in mind, it is easier to appreciate how these brain states can be either dangerous or therapeutically altered. Intoxication with alcohol can be particularly dangerous and lethal when the rate of alcohol intake far outpaces the ability of homeostatic brain mechanisms to counteract the effects of the drug. Similarly, extreme degrees of homeostatic adjustment from prior intoxications can manifest as *extreme levels of overcorrection* when the alcohol is eliminated from the brain, exposing the brain to serious risk of excitatory–inhibitory imbalances, that it does not have time to dissipate (meaning time for *correcting the overcorrection*) before those imbalances produce injury or death. Now comes the utility of **benzodiazepines** for the treatment of alcohol withdrawal. Benzodiazepines affect GABA (A) receptors in a way that is similar to alcohol, and thus they can also produce alcohol-like intoxication and withdrawal syndromes. However, benzos can be leveraged therapeutically against the overcorrection of alcohol (or benzo) withdrawal, by artificially buttressing against and

softening the effects of extreme overcorrection. This then gives the natural "correction of the overcorrection" more time to take place, without it involving a precipitously dangerous phase of excitatory instability. In this way, the benzo is simulating to some extent the original effects of the intoxicating alcohol, so the benzo is in essence lessening the degree of physiological severity of the overcorrection in exchange for prolonging how long the "correction of the overcorrection" takes place. As you might imagine, the efficacy of this approach depends heavily on the initial dosing and rate of the **benzodiazepine taper** (scheduled dose reduction over time), which requires appropriate, skilled clinical monitoring and decision-making.

Notably, the use of various drugs of the wider **benzoid** family that all enhance GABA (A) receptor activity (including benzodiazepines like lorazepam, barbiturates like pentobarbitol, or "atypical" benzodiazepines like zolpidem) that can medically treat withdrawal syndromes produced by alcohol or prior benzoid use is technically not really a **detoxification** process as it is often called. Indeed, these withdrawal treatments are actually a kind of temporary *re-toxification*, happening in a controlled way, while the body itself is doing the real work of detoxification (meaning getting rid of the offending chemical and its effects). The only kinds of actual medical detoxifications that fit the title are those techniques that actively assist in getting the drug out of the body like gastric lavage or hemodialysis. Thus, inpatient units that say they provide "detox" actually only treat withdrawal syndromes in ways that allow the body itself to *safely* detox, as facilitated in the case of alcohol withdrawal, by a clinically guided re-toxification with benzoids.

As alluded to previously, all intoxicating substances, even the relatively safe and nonaddictive ones like caffeine, have a withdrawal state. In addition, every intoxication (however subtle) is followed by some degree of withdrawal (however subtle, if not totally unnoticed, it may be). But in general, as with the old saying "the bigger they are, the harder they fall," the bigger the intoxication episode was, the bigger the withdrawal will be. Also, the longer an individual has been in a state of sustained intoxication over time, the more severe and prolonged the withdrawal phase will be. Fortunately, although most university students will experience a hangover (multiple?), few will experience alcoholic seizures and DTs. Nevertheless, both everyday hangovers and DTs are forms of alcohol withdrawal.

With respect to these rules of thumb about intoxication–withdrawal syndromes, it is important to keep in mind that just as different types of addictive drugs have differing and even contradictory intoxicating states, they will also have different withdrawal states. So, as CNS depressants tend to have excitatory withdrawal states, CNS stimulants tend to have depressant-like withdrawal states. The exact biophysical nature (anatomy, receptor systems, and directionality of homeostatic changes) that a given drug may evoke in the intoxication/withdrawal transition differs from one drug to the next. Thus, alcohol acutely provokes GABAergic receptor activation, whereas caffeine acutely decreases activation of the **adenosine** receptor. In contrast, the correlating homeostatic compensation to caffeine upregulates the adenosine receptor. This adenosine upregulation leads to caffeine's famous withdrawal state – the mid-afternoon postcoffee energy slump. There is a whole diversity of these kinds of effects depending on the drug. Interestingly, for example, chronic nicotine actually *upregulates* **nicotinic acetylcholinergic** receptors (creates more of them on neurons) while at the same time it desensitizes them (makes each one less powerful at invoking a postsynaptic neuronal effect).

Although the clinical pictures of intoxication and withdrawal are largely opposite, the changes from sobriety through one state to another is a gradual transition (on the order of minutes to hours) happening across four phases as shown in Figure 2.1 and outlined below:

Phase A: Normal baseline (sober)
Phase B: Drug-entry–induced inclines in receptor activation (intoxication)
Phase C: Homeostatic compensations attempt to mitigate phase B (mixed state)
Phase D: Homeostatic corrective activity unopposed by Phase B (withdrawal)

Notably, as shown in Figure 2.1, these phases also show variation in their dynamics based on not just the amount of drug that is being used in a given episode, but also depending on the historical context and recent pattern of the individual's substance use. Thus, Figure 2.1 also begins to illustrate the biological and clinical interdependence of the triad of intoxication, withdrawal, and tolerance.

The ***pharmacodynamics*** (referring to how changing drug levels produce changing downstream biological effects on the brain) underpinning the effects and interrelationships between intoxication, withdrawal, and tolerance (as shown in Figure 2.1) is fairly universal

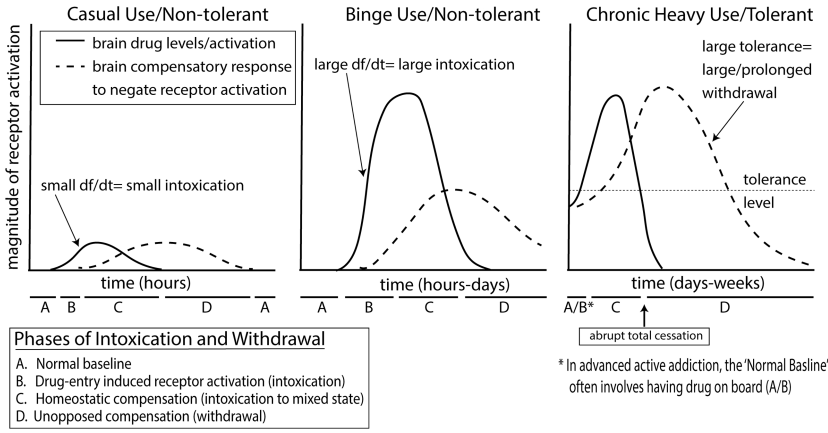

Figure 2.1 Interrelationships between intoxication, withdrawal, and tolerance across stages of addiction severity.

across all the major addictive drug types, even though the cellular and molecular biology by which these different drugs evoke their effects may differ considerably. So, for example, Figure 2.1 is conceptually applicable to alcohol as well as opioids. Let's consider some of the underlying biology of the pharmacodynamics of opioids as a contrast with what we have already described for alcohol. Although there are different neurochemicals, receptors, neuronal cell types, and neurocircuits in play in the effects of opioids as compared to alcohol (which is what makes opioid intoxication quite qualitatively distinct from alcohol intoxication), the same general rules that relate intoxication, withdrawal, and tolerance to each other (Figure 2.1) are true for both drugs.

Opioid Intoxication and Withdrawal

Corresponding to Figure 2.1, Phase B (intoxication), **mu opioid receptor** activation by **exogenous opioids** (drugs being ingested, that powerfully mimic the effects of **endogenous opioids** that our nervous systems naturally produce), leads to decreased neuronal excitability, and thus decreasing signaling, through ascending pain pathways (chains of interconnected neurons, from the periphery to the sensory cortex). This happens as a result of mu opioid receptor activation producing decreases

in **cAMP signaling** (a key intracellular, G-protein–coupled messenger molecule) and voltage-gated calcium channel activation within individual neurons in the relay. Similar affects happen in (a) upper level **thalamo-cortical relays** that end up blunting the representation of pain in cortical-sensory regions (hence blunting the levels of conscious awareness of pain); (b) striatal and limbic/emotional pathways that induce effects underpinning states and feelings of relaxation and calm; and (c) sympathetic nervous system pathways that end up blunting autonomic "fight or flight" responses that would normally be generated in situations where the body is being injured. Now, with high levels of exogenous opioids floating around in the CNS, the brain starts engaging a variety of homeostatic compensatory mechanisms corresponding to Figure 2.1, Phase C. Cellular mechanisms kick in that counteract the mu receptor activation effects on cAMP pathways and voltage-gated calcium receptor response systems (which depress neuronal activity), including but not limited to efforts that upregulate excitatory neurotransmission in these pathways (much of which is medicated by the excitatory transmitter glutamate). Next, corresponding to Figure 2.1, Phase D, the body is now successfully removing and eliminating the exogenous opioids from the brain, but we now have the homeostatic changes intended to counteract the opioid effects left over, increasingly unopposed by opioids. This results in *increased* neuronal excitability in the same sensory, limbic, motor, and autonomic pathways that were initially depressed by the mu opioid receptor activation (of opioids), now generating the common withdrawal symptoms of increased pain, dysphoric mood, diarrhea, restlessness, muscle spasticity, tearing/crying, goose bumps, elevated pulse, elevated blood pressure, and so on. An important clinical implication of all this, relevant to the use of chronic opioids for chronic pain, is the phenomenon of **opioid-induced hyperalgesia**, where the cure, if applied for too long, becomes a part of the disease. People taking opioids long term for chronic pain experience profound sustained blunting of the endogenous opioid system with *increased* pain sensitivity (above and beyond what the original injury may have produced) whenever they are not acutely intoxicated and whenever they enter a state of opioid withdrawal. This opioid-induced hyperalgesia is a manifestation of opioid tolerance, and a sign that the patient will experience very severe withdrawal if taken off opioids,

sometimes occurring as part of a pathological iatrogenic process of worsening pain and opioid addiction.

Pharmacokinetics in Intoxication and Withdrawal

There are multiple factors that can affect an individual's degree of intoxication when given a set dose of a drug such as weight, gender, individual biological differences, and current level of substance tolerance. However, a major determinate of intoxication level that is somewhat separate from these individual factors pertains to the **pharmacokinetics** of drug delivery (the levels and *rates of change* of drug levels in the brain). There are three main pharmacokinetic factors that affect the level and quality of intoxication: (1) quantity absorbed; (2) rate absorbed/route of consumption; and (3) rate of elimination:

(1) Quantity absorbed. Generally, the more substance taken, the greater the brain receptor impact that "pushes" the intoxication (across all of its symptom domains). Assuming similar tolerance levels, a person who drank three beers in a half hour on an empty stomach (greater absorption from the stomach) would have greater intoxication than a person who drank one beer in half an hour with pizza (a lesser quantity absorbed). An interesting caveat to this "more is more" rule is that certain drugs, for example, those with **partial agonist activity**, can have a ceiling effect where after putting a certain amount of the drug into the brain, there is not much more that higher doses will do. Thus, if the dose of drug delivered to the brain is so high that nearly all of the brain's receptors are covered by the drug (and all the receptors are only partially activated), then putting more drug in won't accomplish much more. This drug-specific property can have real medical implications and confer added safety to a drug. For example, delta-9-THC (**tetra-hydrocannabinol**), a main psychoactive ingredient of marijuana, and **buprenorphine** (opioid treatment for opioid addiction) both have this characteristic, which means that lethal overdoses on marijuana alone or buprenorphine alone are basically non-existent.

(2) Rate absorbed/route of consumption. The faster a substance gets in the body, the steeper the incline in blood (and brain) levels of the drug. This greater "acceleration" of receptor-level effects more readily outpaces and overwhelms the homeostatic compensations that are happening (that the brain is implementing while trying to reverse the intoxication), which kicks

in only after intoxication begins, and requires its own time to develop. Assuming similar tolerance levels, a person who drank five beers in an hour would have far more severe intoxication than a person who drank five beers over five hours (one beer per hour). In this way, the rate of rise of the drug in the blood (brain), is the slope (remember calculus?) – that is, the first derivative (df/dt) of the drug level curve, f(t) (see Figure 2.1). This slope plays a huge role in the degree of intoxication, even more so than what the instantaneous level or magnitude of the drug in the brain determines. Because of this dynamic, individuals on the upslope (positive first derivative) of the blood level curve (at time "a") are generally much more intoxicated on the drug, compared to later on when the drug levels at time "b" – measured as being quantitatively the same as at time "a" – are declining due to metabolic elimination, with the curve now on the back downslope (showing a negative first derivative).

The **route of consumption** is a key determinant of the rate of absorption of a given drug into the bloodstream, which works along with behavioral measures of rate of consumption to determine intoxication severity. The route of substance entry into the body greatly determines how rapidly it gets into the blood, and this in turn impacts how rapidly concentrations rise in the brain to produce a higher df/dt (upslope of drug level curve). Generally, more direct and efficient routes of bloodstream entry, where the drug contacts a larger blood volume per unit time, produces more rapid rates of rise (e.g., intravenously (iv) > smoked > oral > transdermal). Thus, assuming similar tolerance levels, a person who injects heroin iv would have greater intoxication than a person who snorted *the exact same amount* of heroin. Figure 2.2 illustrates this point.

As addiction disease severity worsens over time, the individual will not only behaviorally consume more of the drug, but they will often change their route of use to be more efficient and intoxicating, so that a greater df/dt in the drug level curve is achieved. For example, a typical trajectory in opioid addiction occurs when a person misuses opioid pills by oral ingestion for several months then transitions to crushing and snorting pills for a year, then injects crushed pills, then moves on to iv use of high potency opioids and/or heroin.

(3) Rate of elimination. How fast the drug is broken down and removed (metabolized) from the body (a lot of which happens via liver and/or

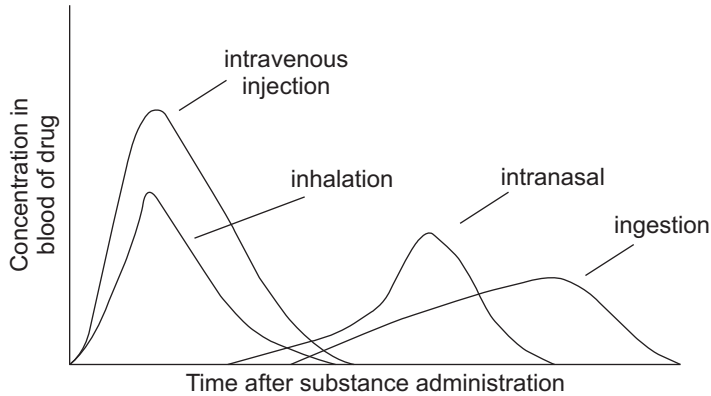

Figure 2.2 Relative timeframe for blood concentration of substance per route of use.

kidney) is separate from the many homeostatic mechanisms operating in the brain that try to counteract intoxication. Both of these forces are in play simultaneously as intoxication is happening, in an effort to blunt intoxication, like a parallel race between counteracting pharmacokinetic and pharmacodynamic forces. Both the behavioral manner of cessation of use and rate of elimination (metabolism) determine how fast the blood/brain levels of the drug are in decline, which can in turn impact how severe and prolonged the withdrawal syndrome is. Of course, withdrawal syndrome severity and quality and how it interfaces with the initial intoxication phase is affected also by the extremity of brain homeostatic changes invoked to counter the initial intoxication (and history of prior chronic intoxications). Thus, the rate of elimination of a drug can impact both the intoxication and withdrawal phases. An interesting factoid about alcohol is that its rate of metabolism is not only reliably linear, but is fairly consistent across humans with relatively intact livers, despite age or body size differences. A rule of thumb is that a person who has stopped drinking loses about 0.015% of their blood alcohol concentration per hour (regardless of where they started) so that it will take about 5 hours to go from the common legal limit of 0.08 to 0.0. With serious liver disease, this rule of thumb will likely be invalid, showing much lower rates of elimination.

The key concept here is that intoxication level is much more than a simple reflection of the level of drug in a person's blood at a given

time; it is also greatly determined by how quickly that blood level is rising (or falling). Comparing the casual use/nontolerant condition in Figure 2.1 to the binge use/nontolerant condition illustrates how a heavy binge-drinking episode results in a steeper slope and greater magnitude of intoxication-related receptor changes than a milder, typically "socially acceptable" drinking phase does. Additionally, the greater magnitude of invoked homeostatic compensations is a set up for experiencing more severe withdrawal symptoms. Each addictive substance has its own unique profile in terms of the duration/severity of its withdrawal symptoms, but the core idea that *increased intoxication results in increased withdrawal symptoms* is generally true across drugs.

Tolerance

Regular use of an addictive substance leads to tolerance over time. Tolerance involves an accumulation of homeostatic brain adjustments, and a kind of longer-term solidification of these changes, that are trying to adapt the brain to the presence of the drug. Brain state changes resulting from the chronic accumulation of homeostatic compensation becomes the individual's "new normal." In this way, tolerance can be conceptualized as a type of chronic homeostasis. And here we can see that acute withdrawal and tolerance are actually somewhat biologically interconnected phenomena, where a series of acute homeostatic changes (that set up withdrawal) become more chronic and long lasting (causing tolerance). Building up tolerance thus sets the individual up for experiencing withdrawal syndromes of greater severity and longer durations if the drug supply is substantially cut down or terminated.

In the past, having high tolerance has been used to refer to (or being the same as) being in a state of "**substance dependence**." So, for example, in this usage, when someone has become dependent on the drug, they have become both tolerant to high doses of the drug, but also *intolerant of not being on the drug* (in terms of being at risk of suffering more severe acute withdrawal). However, the fifth version of the **Psychiatric Diagnostic and Statistical Manual (DSM-5)** removed the term "substance dependence" in part because its meaning had become widely used not just for being in a state of high tolerance and susceptible to withdrawal, but also meaning in a state of having addiction. The problem here is that being addicted to a drug and having tolerance to the drug (i.e., being at risk for acute

withdrawal), although they can often go together, are not at all the same, clinically or biologically. This is easy to understand considering that it can take months to years to fully treat and remit an addiction, whereas treating withdrawal syndromes, and getting out of tolerance, usually only takes days to weeks and may do little to treat the long-term addiction. At the same time, a person can absolutely develop tolerance to a given drug fairly quickly, and yet not at all be addicted to it (e.g., as can happen with blood pressure medicine). So, while the DSM-5 has abandoned the terminology of "substance dependence" to avoid a false equivalence of tolerance with addiction, it has adopted the term "substance use disorders," both as a general umbrella term for the entire spectrum of intoxication, withdrawal, and addiction syndromes, but also referring more specifically to the continuum of degrees of severity of addiction diagnoses. Notably, DSM-5 is actually the first iteration of the DSM in decades (in contrast to several prior consecutive versions) that actually contains the word "addiction". This belated re-entry of the term was a result of fear still held by many people, that "addiction" is itself a stigmatizing term. Even the DSM-5 still seems to show ambivalence about addiction as a stigmatizing term, because although it includes the word as the heading of a collection of disorders (that are addictive disorders) it does not list it with each SUD diagnosis. Thus, alcohol addiction is labeled by the DSM-5 as "alcohol use disorder." It is debatable as to which approach is more stigmatizing, between using or avoiding words that refer to a highly stigmatized disease. (It is the opinion of the authors that greater stigma comes from what people accept or deny about what addiction is as a disease, and how they want to treat it, rather than the letters and words we use to label it.)

As with prior versions of DSM criteria for "substance dependence," tolerance remains one of several criteria in the DSM-5's characterizations of "substance use disorder" (i.e., addiction syndrome). But, in acknowledgment of its false equivalence with addiction, tolerance has been pushed down the list and diluted in influence a bit as a criterion for SUD by the addition of other more important criteria for addiction like "craving." Notably, the old DSM-IV diagnosis of "**substance abuse**" has also been abandoned by the DSM-5, in part because psychiatry decided to reserve the term "abuse" for what people do to each other, not to non-living objects. The word "abuse" also became viewed as unacceptably stigmatizing for people with addictions, because generally, people who perpetrate "abuse"

are generally thought of as bad people. However, "substance abuse," in terms of the syndrome it was labeling, became fairly successful in representing an early or mild form of addiction before serious tolerance to the drug had set in (hence, tolerance was not a criterion for "substance abuse," whereas it was with "substance dependence"). Now with DSM-5, early or mild forms of addiction are understood as synonymous with **mild to moderate substance use disorder** (what used to be called substance abuse), whereas more severe addictions are the same as severe substance use disorders (what used to be called substance dependence).

Tolerance can be succinctly described from a clinical pharmacodynamic perspective as being the name for either of these two essentially equivalent phenomena:

(i) After chronic use, needing more of a substance to have the same intoxication effect as previously.

OR

(ii) After chronic use, the same amount of substance as previous now has less of an intoxication effect.

Thus, tolerance is ultimately related to the same up- or downregulations of receptors (or whatever homeostatic responses are invoked depending on the type of substance) by various states of intoxication. For instance, opioid use causes a higher number of opioid receptors to be activated than would occur naturally (via endogenous opioid release) such that chronic use results in a homeostatically reduced number of available opioid receptors via downregulation. In turn, fewer receptors available contributes to intoxication becoming more difficult to achieve. Again, however, the reader should keep in mind that the biological reality of tolerance is much more complex; there are many biological mechanisms by which tolerance occurs. For example, in addition to receptor density changes, opioid tolerance involves many changes downstream from receptors, encompassing cellular/DNA expression changes, and more broad neural systems adjustments.

As mentioned previously, tolerance, while working to minimize intoxication levels, also magnifies severity of withdrawal. Figure 2.1, in the chronic binge use/tolerant condition, shows how withdrawal symptoms become longer in duration and greater in severity compared to the nontolerant examples. This is because the brain homeostatic changes that have developed in response to the chronic presence of the

drug are more profound, more extensive, and take much longer to re-normalize. *Thus, as tolerance increases with chronic use, susceptibility to intoxication decreases while severity of withdrawal increases*. Often, an individual's addiction first becomes known to medical providers when they experience major withdrawal symptoms that typically also represent a high state of drug tolerance. This can be a great opportunity to try to alleviate suffering and engage patients into long-term addiction treatments described in Chapter 5 under **detox-withdrawal treatment (DWT)**.

As already mentioned, although tolerance is connected with intoxication and withdrawal, it is not really connected much with either the biology or phenomenology of addiction. Tolerance will always resolve (on the order of days to weeks) if substance use stops for an extended period, and this happens regardless of how strong one's addiction disease continues to be (for month to years). Many cases of lethal drug overdose occur when a person who is still addicted (but has been abstaining for some time) relapses onto their usual high dose of the substance that they had previously been tolerant to (but no longer are). This is a frequent dangerous outcome for people who are criminalized for having opioid addiction. They are incarcerated, then released after their tolerance and withdrawal have resolved, but their addiction persists, producing an especially high risk of a lethal overdose.

Basic Criteria, Signs, and Symptoms of Addiction

Whereas intoxication and withdrawal pertain to the acute symptoms that active drug use generates, tolerance is a longer-term process that modulates the severity of intoxication and withdrawal depending on the prior pattern of use. Apart from these phenomena, there exists the even longer-term cognitive, motivational, and behavioral changes that occur in the disease of process of addiction.

Looking at the DSM-5 criteria for substance use disorder/addiction (Table 2.1), consider how the large majority of these criteria (1 through 9) describe changes in cognition and behavior that reflect abnormalities in motivation. Meanwhile, Criteria 10 and 11 describe tolerance and withdrawal, which are going to happen with heavy chronic use as *correlates* of the addiction, but do not really reflect the pathological motivational changes that are core to addiction.

Table 2.1 DSM-5 criteria for a generic substance use disorder (addiction)

Substance Use Disorder (DSM-5)
A problematic pattern of substance use leading to clinically significant impairment or distress, as manifested by at least two of the following, occurring within a 12-month period:

1. Substance is often taken in larger amounts or over a longer period than was intended.
2. There is a persistent desire or unsuccessful efforts to cut down or control substance use.
3. A great deal of time is spent in activities necessary to obtain substance, use substance, or recover from its effects.
4. Craving, or a strong desire or urge to use substance.
5. Recurrent substance use resulting in a failure to fulfill major role obligations at work, school, or home.
6. Continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of substance.
7. Important social, occupational, or recreational activities are given up or reduced because of substance use.
8. Recurrent substance use in situations in which it is physically hazardous.
9. Substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by substance.
10. Tolerance, as defined by either of the following:
    - **(A)** A need for markedly increased amounts of substance to achieve intoxication or the desired effect.
    - **(B)** Markedly diminished effect with continued use of the same amount of substance.
11. Withdrawal, as manifested by either of the following:
    - **(A)** The characteristic withdrawal syndrome for substance (refer to Criteria A and B of the criteria set for substance withdrawal).
    - **(B)** Substance (or closely related substance) is taken to relieve or avoid withdrawal symptoms.

Notice how DSM criteria 1–9 describe an individual who has begun to prioritize substance use over other major domains of motivated behavior such as work, relationships, maintaining physical/mental health, or even other recreational activities. To better organize and recall these criteria, it is helpful to rearrange them as shown in Figure 2.3. The way this figure conceptualizes addiction as something that grows into MORE, while requiring greater TIME and SACRIFICE, readily boils down to the core concept of addiction we introduced in Chapter 1: "*A chronic progressive brain disease producing pathological growth of compulsive motivation resulting in drug seeking and taking, despite accumulating negative consequences*."

Addiction and Sensitization

As we will cover in greater detail in Chapter 3, addiction, as described by DSM-5 criteria 1–9 (Table 2.1) and as conceptually organized in Figure 2.3, is a brain disease that entails an *abnormal growth process*. The abnormal growth happens in terms of the *motivation* to acquire and use more drug. More hits of the drug produce more growth of the motivation for more hits of the drug –

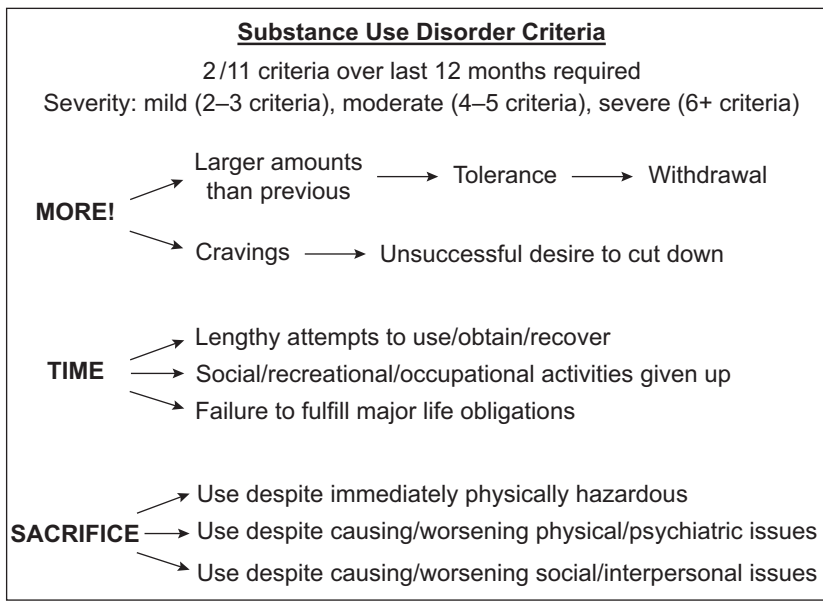

Figure 2.3 Simplified substance use disorder (addiction) criteria.

which produces more behaviors that deliver more hits of the drug . . . and so on. Thus, the growth process of addiction is like a vicious, three-part, auto-reinforcing cycle. It cycles from (1) drug effects on brain to (2) changes in motivation to (3) changes in behavior – which increases the probability of delivering more drug effects on the brain (back to part 1 of the cycle)! The acceleration and increasing compulsiveness of this cycle, occurring as a pathological growth in motivation, is closely related (biologically and behaviorally speaking) to a phenomenon well characterized in the basic neuroscience literature termed **drug sensitization**. In *sensitization, we see an effect that works oppositely from tolerance*. In tolerance, we get a loss of effect of the intoxicating properties of the drug as the individual experiences more drug doses. In sensitization, we get a growth of motivational effects of the drug (toward using the drug again) as more doses of the drug accumulate. Clinically, this growth of motivation can be observed quite vividly not only as fulfilling more and more of the DSM-5 criteria, but as having properties that can be strikingly similar, in a behavioral sense, to having cancer, or even a parasitic infection! But rather than representing a physical mass in the body, like a tumor growing out of control, or being host to a resource-consuming organism that has invaded the body, the disease of addition produces pathological growth and parasitic-like effects within the individual's **motivational-behavioral repertoire**. So, motivations and behaviors encoded and stored in the brain that lead to drug use inappropriately gain prioritization and greater likely hood of being "called up and enacted" in the brain. This leads to more *time spent* on those activities, at *the sacrifice* of many other healthy motivations and behaviors.

Myth-Busters

We will elaborate more on the motivational-behavioral repertoire in Chapters 3 and 4, which will allow us to open the door to describing much more about what addiction disease is on both the neurobiological and **neuroinformatic** (brain information processing) levels. But, as a prelude to this deeper neuroscientific exploration, we should clarify in this chapter more about what addiction disease is not, in terms of debunking four major ideas (or storylines) that have been commonly espoused to explain addictive behavior (or people with addictions), even as they are quite misleading and inconsistent with objective evidence. We call these four storylines Myths, much as ancient Greek

mythology provided storylines to explain an origin or function of a part of the natural world before the advent of modern science and application of objective hypothesis testing. For sure, the ancient myths were attractive and memorable to people and played a role in conveying some kind of message or agenda. But that did not make them scientifically accurate, provable, or useful for building progress in a technology- and science-based system like health care. Discussing these myths, and their inaccuracies, in some detail here will help us get closer to understanding what addiction disease really is behaviorally and neurobiologically. In turn, this myth-busting will help us replace stigma with a scientifically informed, biomedical understanding of the disease that allow us to diagnose and treat it more compassionately and effectively (Chapter 5). As we discuss these four myth-buster themes, the reader might recall times when friends, family, politicians, police, teachers, healthcare professionals, or even one's own thinking was influenced by or reflected these popular myths and stereotypes about addiction.

Addiction Myth #1: Pleasure-Seeking and Hedonism Gone Wild

"Those addicts just want to get high"

Pursuing pleasurable experiences is *a normal* behavior exhibited by all healthy individuals. The pleasure-seeking myth turns this normal behavior into a bad thing and a pathology of excess that is suggested to underpin substance misuse. It holds that people choose to use addictive substances over and over primarily for the pleasure of intoxication. Therefore, "addicts" should be able to overcome this urge to use substances by simply suppressing their hedonism and dutifully selecting other less-pleasurable but morally righteous tasks in life. So, what is wrong with this picture?

First, this myth incorrectly suggests that across different substances, the relative addictive strength of a substance should correlate with the euphoric-intoxicating effects of that substance, that is, the intensity of the "high." Certainly, for a given substance, the route of entry may determine both the level of high and the addiction risk that the dosing route entails (as previously discussed). Also, the quality of the high (or intoxication profile) of a substance may initially play a role in why an individual *starts* using a substance. However, the quality or intensity of

the high across different drugs is not actually predictive of a given drug's addictive strength. For instance, compare nicotine versus hallucinogens. Nicotine is one of the most addictive substances in the world, yet it does not have the pronounced high of opiates, methamphetamines or hallucinogens. In fact, tobacco (i.e., nicotine intoxication) produces little in the way of high or euphoria, giving most first-time users a bit of dizziness or nausea. Tobacco use is known much more for its numerous undesirable effects than for its high – like cancer risk, shortness of breath, yellowing of teeth, impaired sense of taste, bad breath, harmful second-hand smoke, impotence, financial burden (smoking one pack of cigarettes/day at $5.50 = $2,007.50 per year), to name a few. Yet smokers continue to incur these damages, pretty much without getting a high, while persistently failing at trying to quit. In contrast, hallucinogens such as LSD or psilocybin ("magic mushrooms") produce a profound multisensory and cognition-altering intoxication that can be quite euphorigenic. But hallucinogens are much less addictive and less commonly used chronically than nicotine or other illicit substances like heroin or methamphetamine.

Second, this myth suggests that the individual must feel the effects of the intoxication to allow the addiction to develop. However, human subject drug-administration studies, such as those done by Lamb et al. (1991) and Fischman and Foltin (1992), showed that when blindly given the choice between very low-dose addictive substance (morphine, cocaine) versus placebo, human subjects were more likely to choose the addictive substances even though their low doses caused no detectable physical changes (like increased heart rate or dilated pupils) or even subjective pleasure. Often, these subjects could not reliably guess which choice option contained the addictive substance. Thus, patterns of prioritizing an addictive substance occur even when substance use is separated from pleasurable experience.

Finally, the myth suggests that if a substance becomes less intoxicating over time (e.g., with tolerance), then addictive behaviors would decrease accordingly and basically auto-extinguish. But the opposite is true with addiction. As continued substance use escalates, so do the cravings and addictive behaviors, yet the high becomes weaker with increasing tolerance to intoxication. *Thus, as addiction progresses, pleasure from substance use becomes more short-lived and diminished in intensity while the negative consequences of substance use drastically increase and*

accumulate. Chronic daily drug users with severe addictions will often admit they can no longer get "high" due to this increased tolerance, and yet finding and using the drug remains one of the strongest motivations they have. Conversely, many addiction patients will also report that their first ever use and high of a given drug was by far their best, and something that they never could quite get back again, even when they subsequently used hundreds or thousands of times. So ironically, and in direct conflict with the pleasure-seeking myth, *many patients experienced their best highs when they were not yet addicted.* Then, once they had become addicted, they were quite chronically burdened by an overarching sense of **anhedonia** (lack of pleasure), which addictive drug use could not remedy. Remarkably, this phenomenon, while being characteristic of addiction disease, is not even drug specific, further suggesting that it has little to do with intoxication-euphoria. In fact, the phenomenon may not even require an intoxicating drug at all. For example, in the behavioral addiction of pathological gambling, many patients report that they feel like their illness started with a big win experience, followed by a compulsive effort to obtain more big wins in the face of accumulating losses.

Addiction Myth #2: Negative Reinforcement/Avoiding the Uncomfortable

"Those addicts just use to avoid withdrawing"

This myth argues that people use addictive substances repeatedly primarily to avoid the uncomfortable symptoms of withdrawal that would occur if they stopped use. At face value, this idea seems to make a lot of sense; we all know what it's like expending efforts trying to avoid unpleasurable states. So, what is wrong with this view as an explanation for addiction?

First, this myth suggests that the severity of withdrawal a drug could generate should then correlate with the addictive potential of that substance. However, this is not the case. For example, consider the addictive potential of nicotine. Although nicotine withdrawal can be vaguely unpleasant (it might produce headaches, sleep problems, irritability, and so on), this discomfort pales in comparison to the severity of withdrawal from opiates (diarrhea, vomiting, more pronounced sleep problems, general achiness) or alcohol (high agitation, tremors, seizures resulting in death). Similarly, the withdrawal states of cocaine and

methamphetamine are much less pronounced than those of alcohol or opioids. Yet, nicotine, cocaine, and methamphetamine are generally much more addictive than alcohol. Additionally, there are plenty of psychoactive medication classes like anticholinergics, antihypertensives, or SSRI (selective serotonin reuptake inhibitor) antidepressants that can produce withdrawal states but do not produce addiction.

Second, this myth implies that an individual's cravings for a substance would be highest when withdrawal symptoms are most severe. Again, this is often not the case. Patients often report that cravings are highest shortly after intoxication (or the drug use episode) begins, which is when withdrawal symptoms would be least likely to be present. So, substance intake itself in the early phases of intoxication can spark even stronger cravings for further use. This is why the plan to "just have one little drink . . ." often falls apart for people with alcohol addiction, sometimes resulting in very heavy binging and drug use consequences.

Third, this myth suggests that treating an individual's withdrawal should effectively treat their addiction. Thus, by the logic of this myth, if a person was past their withdrawal phase, they would be cured of their addiction. Unfortunately, this does not happen. Addiction disease persists chronically despite extended periods – even months or years – of abstinence, long after withdrawal is over. A relapse in a long-time abstinent individual is not prompted by any withdrawal symptoms. Many people with addiction are more vulnerable to relapse *after they get through withdrawal* than when they were in it. Consider this not uncommon clinical scenario: a middle-aged male enters the outpatient addiction psychiatry clinic having received inpatient alcohol detoxification three times within the prior two months. His daily alcohol use, a fifth of vodka plus 2–6 beers, would restart about 4–7 days after he went home from each inpatient stay. The patient had a history of alcohol withdrawal seizures and knew that restarting alcohol use would put him at risk of this happening again and lead him to even more episodes of having to go into withdrawal. Yet he relapsed again and again after having endured and completed multiple withdrawal episodes. So, not only was he more likely to relapse after withdrawal, *but the only thing that was making him go repeatedly through the suffering of withdrawal was continued drug use.*

Finally, this myth implies that if an addictive substance could somehow be stripped of its capacity to lead to withdrawal, then it would cease to be addictive. Again, this is not the case. Research looking at centrally

administered addictive substances (i.e., given directly into to the animal's brain in areas that govern motivational control but are not able to generate withdrawal syndromes) show that this delivery is sufficient to generate the development of addictive behaviors. Thus, patterns of prioritizing addictive drug use over placebo occur even when the drug use is separated from the possibility of a withdrawal experience.

Addiction Myth #3: Self-Medication/Alleviating the Uncomfortable

"They are just taking substances to treat their mental illness"

This myth is closely related to Myth #2 in that people in both circumstances are thought to be using substances to alleviate uncomfortable conditions. However, the self-medication hypothesis is specifically applied to explaining substance use in people with mental illness. Instead of it being a state of drug withdrawal they are treating with the substance use, patients are presumed to be alleviating a psychiatric symptom(s), or the side effects of psychiatric medications. This myth is probably the most widely espoused idea for explaining high rates of substance disorders in mentally ill people, not only among patients, but unfortunately as propagated even among many doctors and researchers. So, how does this myth fail? In understanding the shortcomings of the self-medication hypothesis in explaining substance use in mental illness, it is important to emphasize that the issue is not that self-medication does not exist. It definitely does (e.g., a person taking ibuprofen for a headache is clearly "self-medicating"). The issue is that self-medication is not an empirically supported explanation for understanding SUDs in mental illness (on either neurobiological (see Chapter 4) or clinical–epidemiological grounds), and its influence in health care and psychiatry has had significant negative consequences on patients and efforts to integrate mental health and addiction care (as described in Chapter 5). Several of the major failures of the self-medication hypothesis are elaborated on in the following points.

First, the logic of the self-medication hypothesis suggests that if a person were cured of the bothersome psychiatric condition they are self-medicating (by use of addictive drugs), their continued use of the addictive substances would stop. This is generally not the case. When a patient has both a mental illness and a substance use disorder, treating the mental illness alone while ignoring the addiction not only does not

treat the addiction, it often hinders success in treating the mental illness. Even when mental health treatment does succeed in reducing psychiatric symptoms, the addiction(s) usually persist. For example, a person misusing alcohol under the claim that they are drinking it to help with falling asleep (to treat insomnia) will likely not stop the alcohol addiction pattern just because they were given a benzodiazepine or even a breathing assistance machine to treat their obstructive sleep apnea. Certainly, addiction commonly develops in young adults in connection with the emergence of, or worsening of, a mental illness. But this association does not establish causality consistent with a self-medication logic (e.g., it does not mean the substance use is happening as an attempt to treat the mental illness).

Second, the self-medication hypothesis ignores the powerful and well-known (i.e., empirically overwhelmingly supported) evidence about the effects of various addictive drugs (via their intoxicating profiles) to potently generate and/or worsen psychiatric symptoms. Consider the effects of marijuana and amphetamines to produce psychotic range symptoms in otherwise healthy people and *especially* mentally ill people. How could it be then that so many people with primary psychotic disorders like schizophrenia show higher rates of substance disorders involving these substances compared to the general population (from four- to eight-fold higher rates!). Certainly, it is logical (and is empirically well-supported) to posit that these drugs may be worsening their underlying psychiatric symptoms, therefore, making people who are using these drugs more likely to be diagnosed with a psychotic disorder. However, this quite logical and evidence-based assertion is exactly the opposite of what self-medication describes. It is not only not evidence-based but frankly illogical to say that patients are "self-medicating" with substances that clearly, objectively, worsen psychiatric symptoms.

To extend this point further, also consider that, as we have reviewed previously, chronic use of an addictive substance typically involves tolerance to the intoxicating effects of a given drug (that are posited by "self-medication" to be the desirable "medicinal" effects) while the undesirable withdrawal-related effects of the drug *increase* over time. Under these conditions, we can see that chronic drug use can also be accurately understood as causing or worsening psychiatric symptoms rather than treating them. Again, the "alcohol-use-to-help-me-sleep" scenario is a good example of this phenomenon. Whereas the patient

may claim they are "self-medicating" their insomnia by having a few drinks before bed, their heavy alcohol use is actually producing insomnia (by putting them into low-grade alcohol withdrawal and waking them up) in the middle of the night. So, in effect, what the patient wants to describe as the cure is in fact part of the disease. Something very similar to this happens with chronic benzodiazepines and chronic opioids. When taken chronically for anxiety and pain, respectively, the real long-term pharmacological consequences of these drugs, due to growing tolerance and accumulating withdrawal vulnerability, is actually to generate more anxiety and more pain (hyperalgesia).

Third, the self-medication hypothesis, as it is applied to explain substance use in mental illness, falsely explains drug-taking behavior as reflecting a strong motivation by patients to alleviate their symptoms. However, the empirical evidence tells us that dual-diagnosis patients in active use (e.g., those with mental illness who are currently using drugs) are, compared to non–substance-using mentally ill patients, *actually less able and likely to self-medicate their psychiatric symptoms with medications that actually work!* Hence the self-medication hypothesis is often used to explain behavior in a population that is well characterized as being especially unable to effectively self-medicate! Indeed, heavy, chronic use of virtually all addictive drug types disrupts and reduces the beneficial therapeutic effects of essentially all the major psychiatric medication classes (antidepressants, mood stabilizers, and antipsychotics).

Fourth, self-medication, if it were really true, would be expected to cause an alignment of certain types of substance use with certain types of mental illness. By the logic of self-medication, a matching alignment would be expected to emerge in the epidemiology of dual diagnosis, where the known intoxicating effects of a given drug would explain that drug's specific linkage to a particular type of mental illness, or symptom set, that a given intoxication would be expected to treat. Although this kind of observation does occur in the epidemiology to link certain evidence-based medications with certain psychiatric disorders (e.g., we do observe the taking of antipsychotics as being more common in patients with schizophrenia compared to other illnesses), epidemiological data do not support such *drug-specific* linkages between certain types of mental illness and certain types of substance use patterns. What we actually see is a very different overarching rule emerging in the epidemiological data (see Chapters 1 and 4). Generally, the magnitude of mental illness severity

(regardless of type of mental illness) predicts greater risk and severity of having one or more addictions, generally *across classes* of addictive substance types. In other words, most major mental illnesses incur greater risk of addiction (over general population levels), and this addiction risk is not specific to any one type of addictive drug or intoxicating profile. As we will discuss in some neurobiological depth in Chapter 4, this theme is indicative of a causal, neurobiological connection between *addiction and mental illness*, not between intoxication and mental illness symptoms per se, except to the extent that certain intoxication and withdrawal syndromes can readily mimic and worsen specific mental illness symptoms (which is also not consistent with self-medication). Thus, although the epidemiology of dual diagnosis does not support the idea that substance misuse in mental illness reflects behavior that is about "medicating symptoms," these data indicate the need for an alternative neuroscientific theory that better explains why mentally people are so susceptible to using drugs that so clearly make their illnesses worse. This *neuroscience of addiction psychiatry* is described in Chapter 4.

Fifth, the "self-medication" myth ignores and distracts patients and healthcare professionals away from recognizing, preventing, and treating the disease of addiction, even as it is occurring in its most severe and deadly forms in people who are among the most vulnerable to the disease: people with mental illness. This problem may rank as the most clinically harmful implication of the self-medication hypothesis, in that by essentially conflating what is a comorbid disease with a "medicine," mental health patients are unable to get legitimate addiction treatment, and behavioral health professionals are unable to provide it. In effect, the "self-medication" hypothesis actually relabels and reframes drug-taking behavior (which is actually happening in a damaging, addicting pattern, reflecting a comorbid disease) as a good or medically reasonable thing to do. In this way, the self-medication hypothesis, as it has been widely adopted in its various forms in psychiatry and medicine, has at times done tremendous harm by co-opting the healthcare system into not only ignoring addiction, but in taking an active role in supporting its spread and even causing the disease! For example, in psychiatry, the tobacco industry has been significantly influential in supporting research, psychiatric professional opinion, and even access to tobacco for mentally ill people by promoting the idea that nicotine use is very frequent in mental illness *because* it is a medicine for various

psychiatric disorders. The industry literally funded the self-medication myth in psychiatry. This has had the devastating effect of preventing the adequate diagnosis and treatment of nicotine addiction specifically in patients who actually have the most severe forms of it and are dying at the most extremely high rates from it.

In a more general sense, the widespread endorsement of various versions of "self-medication" explanations by mental health professionals and researchers has unfortunately also served as a way for professionals to excuse themselves from, and avoid, taking responsibility for diagnosing and treating (or researching addiction) in mentally ill patients. Ironically, this may in part reflect an effort to avoid double stigmatizing their patients with two highly stigmatized diagnoses: Many providers (and patients) would prefer to label patients as having mental illnesses who are "self-medicating" rather than diagnosing mental illness with drug addiction. In this way, we can understand how the self-medication myth persists because, as with other myths, it does have an attractive utility and agenda. However, although it may reflect an attempt to avoid a stigmatizing labeling of patients, it may also reflect a deeper stigmatized attitude toward addiction by professionals (**professional stigma**) and patients (**self-stigma**). Denying that addiction exists (sweeping it under the rug or covering it up) and not treating it where it does exist is actually a form of **label avoidance stigma**, whereas the lack of addiction services in mental health services represents **structural stigma**. Interestingly, label avoidance stigma, in the form of patient minimization and denial of the disease, is also a symptom feature of addiction disease itself! Lack of insight and judgment pertaining to addiction disease severity and illness-related behaviors in patients that cause them to attempt to cover up and hide their addiction (from themselves and others) are classic psychological features of addiction that also reflect neurobiological–anatomical dimensions of the disease (see Chapter 3).

Unfortunately, the profound influence of the self-medication hypothesis across the psychiatric community has adversely impacted efforts in building integrated addiction and mental health services and enlarging the field of addiction psychiatry. Yet, an even more florid, broad-based, and devastating example of how self-medication mythology can adversely substitute for and distract healthcare professionals from understanding and addressing addiction is illustrated by the advent of the iatrogenic opioid epidemic beginning in the US (circa 1995 to present). In this crisis, doctors and

healthcare systems, via the overprescribing of opioids and other addictive drugs, instigated unprecedented levels of illness and death due to overdoses and other addiction-illness death trajectories. At the early origins of this epidemic, several myths were created and propagated by medical professionals, drug companies, large hospitals, and hospital regulatory organizations that supported this overprescribing. One was the idea that pain should be considered a vital sign. Another was the idea that having pain would protect one from getting addicted. As an extension of this latter notion, a novel medical diagnostic construct was created, "**Pseudoaddiction**," which was actually closely tied to the "self-medication" myth conceptually and in terms of its detrimental effects on healthcare and patients by distracting away from the reality of the disease model of addiction (see Table 2.2). Pseudoaddiction was designed as a diagnostic label that essentially gave prescribers permission to reframe behavior that looks like addiction as an act of self-medication. Hence "pseudoaddiction" ("pseudo" as in "fake"-addiction) was coined as a term in 1989 to help argue that a patient taking opiates prescribed by a doctor for pain should not be diagnosed with addiction, even if, *and especially if*, they are showing drug-seeking behaviors. Further, it was suggested that the treatment of patients with "pseudoaddiction" (defined as those who look like they have addiction but should be understood as just having uncontrolled pain) was to give even more and higher doses of opioids. Remarkably, proponents of pseudoaddiction (including many who had ties with opioid manufacturers) suggested that failing to treat patients who had "pseudoaddiction" with *more opioids* was unethical and equivalent to producing iatrogenic harm! The term pseudoaddiction, which was never empirically verified as a true medical entity, was part of a large myth-based campaign that facilitated and justified the prescribing of more and more opioids, at higher doses, for longer durations and for more indications, resulting in larger profits and financial benefits to the healthcare system as a whole. Sadly, virtually all sectors of the US healthcare industry, even beyond pharmaceutical companies, have benefited tremendously (i.e., financially) as a consequence of the emerging public health crisis of injuries and medical diseases resulting from iatrogenically caused opioid addictions.

Table 2.2 Comparison of construct attributes of pseudoaddiction, self-medication, and addiction

Concept perspective	Pseudoaddiction	Self-medication	Addiction
Patient's mode of drug-taking	Voluntary/elective	Voluntary/ elective	Involuntary/ compulsive
Patient's decision-making	Intact and rational	Intact and rational	Impaired and irrational
Contextual basis for patient's drug-seeking	Pain symptoms	Psychiatric symptoms	Drug-associated cues
Patient's incentive for drug-seeking and use	Pain symptom relief	Mental illness symptom relief	Chemical stimulation of brain reinforcement system
Presumed value and consequences of drug-taking	Beneficial (symptom relief from pain)	Beneficial (symptom relief from mental illness)	Detrimental (medical and psychiatric harm)
Medical model framework for drug-taking behavior	Drug use = treatment	Drug use = treatment	Drug use = disease
Common attitude engendered	Sympathetic (accepted)	Sympathetic (accepted)	Stigmatized and criminalized
Primary clinical response to drug-taking	Support	Ignore or support	Attempt to stop or reduce
Primary research orientation toward addictive drugs	Focus on/develop therapeutic effects	Focus on/ develop therapeutic effects	Focus on/ develop addiction treatments

Adapted from Chambers and Green (2016) (open source).

Addiction Myth #4: Amorality/Personal Defect

"Those criminals and sinners deserve what they get"

The amorality myth argues that people with addictions lack virtuous characteristics such as morality, willpower, respect for justice, religious devotion, and so on. This line of thought assumes that good/regular people are immune to such disreputable behaviors, creating an ideology that devalues and dehumanizes individuals with addiction. This mindset, resourced directly from stigma, concludes that addiction is a self-imposed criminal condition, and therefore, afflicted individuals *are getting what they deserve*. This myth of addiction has quite universal human appeal, probably originating in part from the anger we can feel when we see the harm that addiction is doing to the afflicted person and their loved ones. However, adherence to this myth has many very serious failures and consequences that do not solve, but actually work to compound the problems of addiction.

First, the amorality myth implies that only bad people try drugs and get addicted, whereas good people never actually try the drug in the first place (and therefore the good ones avoid getting addicted). The fallacy of this idea is made clear when considering the facts that (1) as reviewed in Chapter 1, the vast majority of the US population (who the authors would contend are by and large good people) at some point, for some reason, experiment with and use some form of addictive drug; (2) one's rationale, justification, or decision-making in initially using an addictive drug has nothing to do with and offers no protection against the possibility that an addiction will set in; and (3) no one chooses to get addicted, and the major risk factors for acquiring the disease are both involuntary and of a neurobiological nature, relating to age, gender, genetics, and the presence of mental illness (Chapter 4).

The second failure of the amorality myth is that, even more strongly than "self-medication" or "pseudoaddiction," *it very strongly distracts away from any medical-disease model of addiction, disincentivizing the development and implementation of treatments*, as well as compassion for those who are suffering with the disease. The great danger and harm of this most stigmatizing of myths is that it promotes total neglect and pulls resources away from addressing addiction as a medical problem. Through this neglect and resource drainage it facilitates the spread of the disease, by pretending that it can be and should be dealt with by systematic punishment, such as by incarceration in this life, or the threat of hell in the next. Unfortunately, this view of addiction remains alive and

well throughout the US (and much of the world), as evidenced by the massive investment of US federal and state governments in the failed policies surrounding attempts to criminalize addictive behavior out of existence by means of the "war on drugs" (introduced in Chapter 1). And, as state governments in the US have contended with the growing financial and social costs of mass incarceration, they have had to steadily decrease budget allocations for public education and mental health. Then, as addiction has become widely associated with criminality, it becomes even less associated with the mission or responsibility of the healthcare system. So, doctors, healthcare organizations, and insurance companies are even less likely to support efforts to diagnose it, prevent it, treat it, or research it. They might even actually cause the disease in many patients, and profit from that (e.g., as per the iatrogenic opioid epidemic) while blaming the patients who catch the disease as the "bad apples" (e.g., criminals).

The third failure of the amorality myth is, as a consequence of it being turned into a policy of judgment against a group of people (rather than it pointing to addiction as a diagnosis to be medically treated), is its potential for being used as a political weapon by the community or government to oppress group(s) of people who are easily or misleadingly scapegoated. History has seen this play out countless times with other diseases that were highly stigmatized in the absence of scientific knowledge about the disease (think epilepsy and HIV–AIDS). With respect to the amorality myth in addiction, and its policy fulmination in the "war on drugs," it has been used as a weapon of economic and social oppression against the African American community, poor people of all ethnic groups, and the mentally ill. In the case of the African American community, the amorality myth has been propagated as part of a lie that spread the false belief that black Americans had higher rates of drug misuse, and/or worked as the predominant sources of addictive drugs for the broader community. Thus, criminal legal code was tailored to raise punishments for drug-related behaviors that were specifically associated with being black. In the case of impoverished people, the amorality myth goes hand in hand with the idea that poverty and addiction are attributes of sinful people and so they both naturally and righteously go together. Certainly, although there is an association of poverty with greater rates of addiction, this association is explainable as a consequence of the devastating economic effects of

untreated addiction as it runs in families, and as a reflection of the biological linkage between addiction risk and mental illness, which also has economic consequences. Unfortunately, targeted criminalization of these populations via the war on drugs only worsens the economic and educational status of people in these groups, further locking them into social conditions that increase their likely hood of becoming or remaining poorly educated, traumatized, mentally ill, and disenfranchised from health care. It also delegitimizes the concept of addiction as a biomedical disease entity that requires scientifically informed diagnosis and treatment, insurance coverage, and a professional expert workforce to treat it.

Dispelling Myths with Science Toward Understanding Addiction

So, what do these myths have in common? In one way or another, they all attempt to provide a rationale, logic, or explanatory justification for chronic drug use that we "healthy people" can understand. In Myth #1 it's to feel good; in Myth #2 it's to avoid feeling bad from withdrawal; in Myth #3 it's to avoid feeling bad from mental health symptoms; in Myth #4, it's because addicted people are sinners and criminals, and, well, those people just like to do bad things. As previously mentioned, these myths about addiction are quite similar to what ancient Greek myths were trying to accomplish by explaining natural phenomena as the actions of the gods, as told by stories that **projected** human emotions or motivations onto natural phenomena. Lightning was not understood as a massive discharge of electromagnetic energy based on the accumulation of opposite electrical charges miles apart, it was understood as reflecting the anger or aggression of Zeus – something that can be explained as a projection of a human rationale, explanation, or emotion.

In truth, as backed by behavioral and neurobiological science, the disease of addiction has no rationale or emotional justification, any more than tuberculosis, diabetes, Alzheimer's, HIV, or brain cancers and so on have rationales. All these diseases are just naturally occurring processes that involve progressive biological events that damage and destroy the tissues and function of the individual while causing suffering and loss. With addiction, there is no rationale or reasonable justification for the pathological changes in motivation that drive the

drug-seeking and drug-taking. Addiction occurs and progresses without reason and independent from healthy, or moral, or even immoral motivation or justification. In fact, addiction is a disease that destroys these naturally occurring human motivations rather than representing them. It is irrational, much like psychosis, mania, or dementia are irrational and have no justification. In this way, addiction is appropriately classified as a type of psychiatric disorder, because it involves *loss* of normal motivation, cognition, judgment, emotion, and social interaction – all the things that we view as making up "rational" or otherwise "normal/healthy" human behavior. Addiction is a brain disease that is:

- capable of rendering a previously high-income–earning man unable to hold a job due to alcohol use . . .
- able to cause a person to prioritize methamphetamine purchases over paying rent, despite the risk of homelessness and the recent series of psychiatric hospitalizations due to psychosis that resulted from using . . .
- able to cause a patient with COPD (chronic obstructive pulmonary disease) on oxygen to continue to smoke a pack a day . . .
- capable of causing a pregnant mother to continue to inject heroin daily and smoke cigarettes despite knowing the risks to herself and her future child . . .

As these short scenarios illustrate, addiction (regardless of substance type) has an incredibly powerful effect on causing compulsive drug use despite the damages and losses, even to the extent of disrupting human activities that are critical to the survival of our species, such as maternal motivation and behavior. In peripartum addiction psychiatry clinics, case scenarios like this are tragically common. Rates of pregnant mothers struggling with addiction, often of iatrogenic origins (involving prescription opioids), have been rising massively over the last few decades. In recent years, hundreds of thousands of babies are born annually in the US with prenatal exposure to addictive substances, often involving multiple drug types. Mothers of these children describe how excruciatingly painful it was for them to have their first baby taken out of their arms by authorities due to substance misuse, yet outside of treatment, their use and relapses will continue during their next pregnancy.

The key idea here is that regardless of the type of addictive drug involved, or the particular array of damages compulsive drug use

creates, addiction syndromes are strikingly similar and involuntary, especially as they become more severe. *Thus, the DSM-5 criteria for substance use disorders are essentially the same across all the major addictive substances, even though their intoxication/withdrawal profiles are quite different*. As we will describe in greater depth below and in Chapter 3, this is no accident, because addictive drugs evoke their neurobiological effects in motivational circuits of the brain through similar brain pathways.

Drug Liking ≠ Drug Wanting

At this point in the chapter, the reader is gaining a deeper understanding of how the phenomena of intoxication, withdrawal, and tolerance are fairly interrelated processes. Meanwhile, the chronic motivational changes that occurs in addiction really comprise a different category and timescale of biological and behavioral processes. Now we turn more directly to this question: How does the disease process of addiction develop? Is it gradual and progressive, or does it come in fits and starts? Certainly, the pattern of progression is individualized and depends on a wide array of previously mentioned biological and environmental factors (e.g., genetics, presence and severity of mental illness, age of exposure, and so on). Detection of the exact transition points for someone progressing from casual substance experimentation/use (not a diagnosis) to substance misuse (approximating old constructs of "substance abuse," or in DSM-5, mild SUD) to full-on addiction (moderate/severe SUD in DSM-5) is difficult due to the fact that the progression is fairly gradual (Figure 2.4). Many of the cognitive (decision-making) and motivational changes that underpin addiction are not readily discretely observable. Moreover, the person with

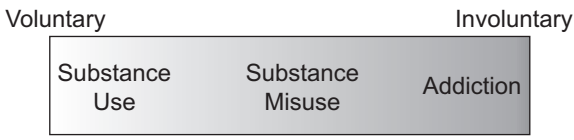

Figure 2.4 Volitional spectrum and progression of addiction. As addiction sets in, it becomes more compulsive and less voluntary or tied to "rational" or normal/healthy decision-making. As more criteria are clearly met for a DSM-5 substance use disorder, substance misuse (i.e., mild SUD (2–3 criteria met) progresses to frank addiction (moderate (4–5 criteria) and severe forms (6+ criteria)).

the growing addiction often works to hide (as a part of the disease process) the behaviors and other signs of the addiction. In this way, the addiction disease not only increases a person's motivation to use, but it also increases a person's motivation to obscure and protect the growth of the addiction! This reminds us again of the cancer and parasitic-like features of addiction, albeit as a progressive disease of motivation.

As described by the paradigm-shifting paper by Robinson and Berridge (1993) – note: this paper is a "must read" classic for anyone entering the field of addiction psychiatry/medicine – there is a simple, clinically relevant framework for understanding how the different key terms and aspects of substance use disorders are (or are not) interrelated. All addictive substances are characterized as having two main categories of effects:

(1) *Intoxication/withdrawal* syndromes ("the Different"):

- **(a)** Symptoms are *acute and can vary greatly* across different addictive drugs.
- **(b)** Use over time leads to *tolerance*; progressive loss of intoxication levels
- **(c)** Associated with *Drug Liking*

(2) *Addiction syndromes* ("the Same"):

- **(a)** Symptoms are *chronic and are similar* across different addictive drugs.
- **(b)** Use over time leads to *sensitization: growth of motivation to use*
- **(c)** Associated with *Drug Wanting*

The "Different" effects of various addictive substances are readily observed when considering how various drug intoxication states are often quite divergent from each other, even to the point of certain comparisons being nearly the opposites (e.g., alcohol versus cocaine). Reflecting this diversity of different intoxicating profiles, we now know that different addictive drugs also have very different and mutually exclusive effects on different regions of the neuroanatomy and cellular receptor systems (Table 2.3, middle column).

On the other hand, these different addictive substances actually cause more of the "Same" effects by activating the brain's motivational and habit-formation circuits, which, in one way or another, involve abnormal (drug-induced) release of the neurotransmitter **dopamine (DA)** into a **basal ganglia** structure called the **nucleus accumbens or NAC** (synonymous with the **ventral striatum**; Table 2.3, right column). With

Table 2.3 Phenomenology and neurobiology of "the Different" intoxication profiles versus "the Same" motivational effects of addictive drugs. Dopamine (DA), Serotonin (5-HT), norepinephrine (NE), nicotinic acetylcholinergic receptor (nAChR), cannabinoid 1 (CB1), mu-opioid (and also to some extent kappa and sigma opioid receptors), $GABA_A$, and glutamate receptor neurotransmission systems are all variously and differentially involved in the diverse intoxicating effects of the major addictive drugs. Different regions and networks of brain anatomy are also differentially impacted by these drugs, producing quite different intoxication experiences (and withdrawal syndromes). Note that in some cases, however (e.g., comparing cocaine to amphetamine), the anatomy and neurotransmitter effects are quite similar, thus leading to similar intoxicating and withdrawal profiles.

Substance	Anatomy of psychoactive effects (intoxication)	Anatomy of motivational effects (addiction)
Cocaine	DA, 5-HT, NE Midbrain, frontal cortex, hypothalamus, striatum	DA Nucleus accumbens
Amphetamine	DA, 5-HT, NE Midbrain, frontal cortex, hypothalamus, striatum	DA Nucleus accumbens
Nicotine	nAChR systems Hippocampus, cerebral cortex, thalamus, striatum	DA Nucleus accumbens
Cannabinoids	CB1 systems Hippocampus, cerebral cortex, thalamus, striatum	DA Nucleus accumbens
Opioids	Mu opioid system Widely distributed in brain, spinal cord	DA Nucleus accumbens
Alcohol	$GABA_A$, glutamate systems Widely distributed throughout the brain	DA Nucleus accumbens

repeated substance use, DA release into the NAC produces a chronic, accumulative impact on NAC neurons and neural networks that represent, process, and store motivational information. As this impact accumulates, it generates an ***abnormal growth process*** **of motivated behavior** (and neural connectivity) that we have already introduced as ***sensitization***. In the growth process of sensitization, the motivation to seek out and use substances grows abnormally. During this growth, many normal/healthy domains of motivated behavior are simultaneously either constricted by or rendered subservient to this sensitization effect, so that they either get knocked out or become *"triggers" for drug motivation.* In this way, the disease process of addiction parallels the insidious destructive growth of a parasite, infection, or tumor within the brain of the individual.

Again, it is important to understand that the "Different" and the "Same" phenomena are quite distinct processes both in the brain and on behavioral levels. Referring again to Table 2.3, we see that regardless of the unique intoxicating effects an addictive drug may have, it still produces some kind of pharmacological impact involving DA release (or related activity) within the nucleus accumbens. This "Different" and "Same" distinction is further reflected by the DSM-5 diagnostic criteria for intoxication states versus SUDs (i.e., addictions). Note that the DSM-5 describes very different intoxication profiles for alcohol use disorder, cannabis use disorder, opioid use disorder, and so on, but in sections describing the criteria for substance use disorders (i.e., addiction spectrum conditions) pertaining to these same drugs, the criteria are essentially the same across these substances. Hence, the different pharmacological–neurobiological effects underlying intoxication fits with the diversity of intoxication syndromes. At the same time, the more similar pharmacological effects of drugs underlying sensitization of drug motivation fit with the similarity of addiction syndromes across drug types. Although this schema reflects a beautifully elegant translation of pharmacological neuroscience to the behavioral level, it is also terribly tragic, given that it illuminates how such a devastating disease could be produced by an array of different psychoactive drugs.

Interestingly, the "Different" versus "Same" schema also extends to the key **subjective experiences** that go along with intoxication versus addiction. People will report that they "like" different types of intoxication

experiences that different drugs produce to different degrees. They may be able to rank order how much they like the high that five different drugs give them, and they can do this based on what they recall about the different qualities of intoxication experiences and how they subjectively felt in those experiences. But all of this has little to do with the "wanting" of these different substances in addiction. The wanting – synonymous with the urge or *craving for the drug* (also now a DSM-5 criteria for SUD) – is not drug- or intoxication-specific. Rather, it is more addiction-syndrome linked, and reflects the experience of longing for, desire for, and excitement surrounding acquiring and using the drug. This wanting/craving is essentially the subjective experience of having the compulsion of addiction. It feels more or less the same, and can be triggered by similar stimuli, regardless of which drug (or intoxicating profile) is involved in the addiction.

Again, these subjective phenomena, "drug-liking" versus "drug-wanting" tend to live under quite different sets of rules in the addicted person. The patient with addiction may say that they really like the high of a given drug "B," even when, in the addicted/active use state, they can't seem to get this full feeling back. Thus, the subjective liking effect remains the same or may diminish with *tolerance*. At the same time, they may have a strong desire to compulsively use another drug, "A," and the craving (wanting) for this drug has grown out of control over time. Thus, this wanting has *sensitized*, and is not even really connected with any appreciation of a high or liking of that drug. In this way, the addiction patient may actually even verbalize *dislike for the substance(s) they are compulsively using despite dedicating large amounts of time, money, and energy to obtaining more.*

This, then, is the power and threat of addictive disease, which grows out of control, involuntarily, like a parasite or cancer to slowly destroy its host. However, with addiction, it is not a literal foreign organism or tumor mass that is growing out of control. Rather, it is the growth of a specific type of motivation (and a pathological change in brain networks that support motivation), in essence causing the host to turn against itself. As illustrated in the following clinical case scenario, and as we explore more in depth in Chapters 3 and 4, this disease process has a real biophysical underpinning as a biological process that strikes young and/or mentally ill brains with particular ferocity.

Case in point: The incredible power of addiction as a disease of motivation. JW used heroin and was admitted to a psychiatric hospital for suicidal ideation. He had a history of multiple intentional and unintentional overdoses. He had been on a ventilator in the past due to overdoses, thus he had a history of showing particularly high risk of lethality with his heroin use, even incurring a prior hypoxic brain injury from overdosing on it in the past. He admitted that he had been disowned by his entire family except for one member due to his drug use. And this one family member and all of his remaining social connections (who were still alive) were active heroin users. Although he had been unable to work consistently in recent years, he once aspired to getting a college education, and had the strong grades in high school needed to get there. But that all changed with his high-school sports injury and the opioid prescriptions. With the onset of addiction, he became jobless and homeless, other than staying on a friend's couch. Recognizing the total devastation opioid addiction had caused him, and the fact that he couldn't even achieve much of a high anymore, he stated he hated heroin for ruining his life and wanted desperately to escape it. But he also knew that if he were left alone, without treatment, with a syringe of heroin on the table, he would want to use it no matter what, even "till death do us part."

BIBLIOGRAPHY

American Psychiatric Association, DSM-5 Task Force. 2013. *Diagnostic and Statistical Manual of Mental Disorders: DSM-5* (American Psychiatric Association: Washington, DC).

Banerjee, N. 2014. Neurotransmitters in alcoholism: A review of neurobiological and genetic studies. *Indian J Hum Genet*, 20: 20–31.

Bruehl, A. M., D. H. Lende, M. Schwartz, C. E. Sterk, and K. Elifson. 2006. Craving and control: Methamphetamine users' narratives. *J Psychoactive Drugs*, Suppl 3: 385–92.

Burkett, J., and L. Young. 2012. Love and addiction: An uneasy marriage? A response to "The devil is in the differences." *Psychopharmacology*, 224: 31–32.

Burma, N. E., C. H. Kwok, and T. Trang. 2017. Therapies and mechanisms of opioid withdrawal. *Pain Manag*, 7: 455–59.

Chambers, R. A. 2009. A nicotine challenge to the self-medication hypothesis in a neurodevelopmental animal model of schizophrenia. *J Dual Diagn*, 5: 139–48.

Chambers, R. A. 2010. Dazed and confused by self-medication. *Am J Psychiatry*, 167: 600; author reply 600–01.

Chambers, R. A., and M. S. Greene. 2016. Physician understanding and treatment of addiction: Have "pseudoaddiction" and "self-medication" led us astray? *J Addiction Depend*, 2: 1–4.

Christie, M. J. 2008. Cellular neuroadaptations to chronic opioids: Tolerance, withdrawal and addiction. *Br J Pharmacol*, 154: 384–96.

Colrain, I. M., C. L. Nicholas, and F. C. Baker. 2014. Alcohol and the sleeping brain. *Handb Clin Neurol*, 125: 415–31.

Davies, M. 2003. The role of GABAA receptors in mediating the effects of alcohol in the central nervous system. *J Psychiatry Neurosci*, 28: 263–74.

de Wit, H., E. H. Uhlenhuth, D. Hedeker, S. G. McCracken, and C. E. Johanson. 1986. Lack of preference for diazepam in anxious volunteers. *Arch Gen Psychiatry*, 43: 533–41.

Fischman, M. W. 1989. Relationship between self-reported drug effects and their reinforcing effects: Studies with stimulant drugs. *NIDA Res Monogr*, 92: 211–30.

Fischman, M. W., and R. W. Foltin. 1992. Self-administration of cocaine by humans: A laboratory perspective. *Ciba Found Symp*, 166: 165–73; discussion 73–80.

Friedman, L., N. F. Fleming, D. H. Roberts, and S. E. Hyman (eds.). 1996. *Source Book of Substance Abuse and Addiction* (Williams & Wilkins: Baltimore, MD).

Gilpin, N. W., and G. F. Koob. 2008. Neurobiology of alcohol dependence: Focus on motivational mechanisms. *Alcohol Res Health*, 31: 185–95.

Greene, M. S., and R. A. Chambers. 2015. Pseudoaddiction: Fact or fiction? An investigation of the medical literature. *Curr Addict Rep*, 2: 310–17.

Harris, R. A., J. R. Trudell, and S. J. Mihic. 2008. Ethanol's molecular targets. *Sci Signal*, 1: re7.

Jensen, E. L., J. Gerber, and C. Mosher. 2004. Social consequences of the war on drugs: The legacy of failed policy. *Crim Just Pol Rev*, 15: 100–21.

Keegan, J., M. Parva, M. Finnegan, A. Gerson, and M. Belden. 2010. Addiction in pregnancy. *J Addict Dis*, 29: 175–91.

Kreek, M. J. 2011. Extreme marginalization: Addiction and other mental health disorders, stigma, and imprisonment. *Ann N Y Acad Sci*, 1231: 65–72.

Kushner, M. G., K. Abrams, and C. Borchardt. 2000. The relationship between anxiety disorders and alcohol use disorders: A review of major perspectives and findings. *Clin Psychol Rev*, 20: 149–71.

Lamb, R. J., K. L. Preston, C. W. Schindler, R. A. Meisch, F. Davis, J. L. Katz, J. E. Henningfield, and S. R. Goldberg. 1991. The reinforcing and subjective

effects of morphine in post-addicts: A dose–response study. *J Pharmacol Exp Ther*, 259: 1165–73.

Lee, M., S. M. Silverman, H. Hansen, V. B. Patel, and L. Manchikanti. 2011. A comprehensive review of opioid-induced hyperalgesia. *Pain Physician*, 14: 145–61.

Lembke, A. 2012. Time to abandon the self-medication hypothesis in patients with psychiatric disorders. *Am J Drug Alcohol Abuse*, 38: 524–29.

Lembke, A. 2016. *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It's So Hard to Stop* (Johns Hopkins University Press: Baltimore, MD).

Littleton, J. 2001. Receptor regulation as a unitary mechanism for drug tolerance and physical dependence: Not quite as simple as it seemed! *Addiction*, 96: 87–101.

McBride, W. J., J. M. Murphy, and S. Ikemoto. 1999. Localization of brain reinforcement mechanisms: Intracranial self-administration and intracranial place-conditioning studies. *Behav Brain Res*, 101: 129–52.

Meldrum, D. R., J. C. Gambone, M. A. Morris, D. A. Meldrum, K. Esposito, and L. J. Ignarro. 2011. The link between erectile and cardiovascular health: The canary in the coal mine. *Am J Cardiol*, 108: 599–606.

Meredith, S. E., L. M. Juliano, J. R. Hughes, and R. R. Griffiths. 2013. Caffeine use disorder: A comprehensive review and research agenda. *J Caffeine Res*, 3: 114–30.

Moore, L. D., and A. Elkavich. 2008. Who's using and who's doing time: Incarceration, the war on drugs, and public health. *Am J Public Health*, 98: 782–86.

Petry, N. M., W. K. Bickel, and M. Arnett. 1998. Shortened time horizons and insensitivity to future consequences in heroin addicts. *Addiction*, 93: 729–38.

Prochaska, J. J., S. M. Hall, and L. A. Bero. 2008. Tobacco use among individuals with schizophrenia: What role has the tobacco industry played? *Schizophr Bull*, 34: 555–67.

Robinson, T. E., and K. C. Berridge. 1993. The neural basis of drug craving: An incentive-sensitization theory of addiction. *Brain Res Rev*, 18: 247–91.

SAMHSA. 2016. *Impact of the DSM-IV to DSM-5 Changes on the National Survey on Drug Use and Health* (SAMHSA: Rockville, MD).

Vaillant, G. E., and M. Keller. 2023. Alcohol consumption. In *Encyclopedia Britannica*.

Weissman, D. E., and J. D. Haddox. 1989. Opioid pseudoaddiction: An iatrogenic syndrome. *Pain*, 36: 363–66.

3

A Disorder of Anatomical Structure and Function: Neurobiology

Learning Points

- **Certain environmental stimuli (natural rewards, stressful events, novel stimuli, addictive substances) are regarded as salient (important) by our brains, triggering a surge of dopamine (DA) neurotransmitter into the nucleus accumbens (NAC)**. This DA surge primes the neural network within the NAC (also known as the ventral striatum) for processing information that controls, changes, and adapts motivation. Motivational representations in the ventral striatum engage and provide hierarchical control over motor representation sequences emergent in the dorsal striatum (caudate putamen, CA-PU).
- **DA surges into the NAC normally facilitate the remodeling (strengthening and weakening) of interneuronal axodendritic connections within the NAC neural network. This neuroplasticity underpins the acquisition of new motivations and the reprioritization of old ones**. Frequently used sets of action representations can become stored and called up as semi-automatic pattern sequences (habits) that form parts of the motivational-behavioral repertoire stored in the neostriatum

(ventral + dorsal striatum). Thus, as certain behavioral patterns are used more frequently concurrent with DA surges into the NAC, these behavioral patterns can become *sensitized* so that they are triggered and executed more efficiently, and with greater priority, but with less demand on neocortical-based cognitive centers and conscious awareness.

- **The ability to store and automatically execute behavioral sequences is highly adaptive and essential to survival. However, addictive drugs can produce abnormally powerful DA surges in the NAC (and have other abnormal neuroplastic effects directly on NAC neurons) that can result in unintentional behavioral patterns getting installed and prioritized, even if they are harmful and maladaptive.**
- **As addiction severity increases, motivation for further addictive substance use increases (i.e., it sensitizes). Simultaneously, various environmental stimuli ("cues"), contexts, or internal brain states previously associated with drug use become more efficient in activating ("triggering") subsequent drug-seeking behaviors**. Such triggering contexts may include locations, people, or states of mind spanning stress, boredom, celebration, excitement, and other affectively charged states.
- **The "amount" of motivation any person has is a limited resource; motivational-behavioral repertoires are large but finite sets. Pathological growth of drug-use motivation will eventually impinge, constrict, subsume, or destroy motivations that guide healthy behavior necessary for life domains and survival (family, work, friends, finances)**. Pathological growth in drug-motivated behavior is clinically observable as the behavioral criteria for addiction (moderate to severe substance use disorder) reviewed in Chapter 2.

Introduction

The Salience of Salience

Salience refers to the brain's assignment of a stimuli or event as being important, worthy of attention, and something that may need to be acted on. The brain is constantly scanning the environment for salience, and it is very good at taking note of salient information. Salience recognition and attribution are key for discerning new and meaningful environmental events and trends and making predictions that should be acted on, sometimes in new ways. If we cannot recognize what is novel, important, and actionable in the environment, then we cannot learn from and act on changes that are constantly occurring in our environments. A lack of adaptability or responsivity to changes in the environment would be readily lethal to individuals and whole species. Hence, brain systems that observe and assess for salience and implement this information for the guidance of motivational control and behavioral action are highly evolutionarily conserved across animals and especially mammalian species. Luckily for our understanding of the neuroscience of addiction, this means that the brain systems that underpin "salience" attribution – which are the "front doors" to addiction pathogenesis – are constructed essentially the same way across rodents, monkeys, and humans! This has allowed us to benefit scientifically from quite accurate animal models of addiction, along with human neuroimaging, to make very deep advances into our understanding of addiction that far surpass anything we currently know about other forms of psychiatric illness. This chapter will describe this multilevel neurobiology of motivation and addiction from the ground up (e.g., from molecules to neurons to neural networks to behavior), providing insights about the clinical syndrome of addiction that are relevant to its diagnosis and treatment.

Back to the salience of salience; there are four main categories of experiential/environmental inputs that our brains find salient:

(1) Natural rewards: food, water, power, money, safety, sex, social connection, winning.
(2) Stressful stimuli: pain, injury, danger, defeat, loss.
(3) Novel/surprising stimuli: something new and different that could be any of the above.
(4) **Addictive substances!**

When experiencing these stimuli or situations, our brains show increased electrical activity (and neurotransmitter outflow) of neurons that live in the **ventral tegmental area (VTA)**. The VTA is a part of the midbrain that is closely related and proximal to the **substantia nigra (SN)**, which projects to the **dorsal striatum**, and is well known as showing progressive degeneration in Parkinson's disease. In contrast to the more famous SN, VTA neurons project their axons into the **nucleus accumbens (NAC)**, which is the ventral territory of the striatum (it *is* essentially the **ventral striatum**).

As mentioned at the end of Chapter 2, VTA neurons project axons carrying the neurotransmitter **dopamine (DA)** into the NAC, which is the primary neural network responsible for managing motivational control and adaptation. In the NAC, DA transmission works in part as a **learning signal** by facilitating **neuroplasticity**, which happens as changes in connection strengths between neurons (within and across large-scale neural networks). Neuroplasticity routinely happens via both the strengthening of connections between neurons (where the synapses between neurons more efficiently transmit signaling power), known as **long-term potentiation (LTP)**, and by the weakening of connections, known as **long-term depression (LTD)**. It is fairly intuitive to relate **synapse strengthening** in LTP to learning new behaviors: repeating a behavior (repeatedly activating neural pathways between neurons that generate the behavior) makes both the pathway and the behavior "stronger," so it can be more easily accessed and efficiently performed in the future. When ancient humans experimented with behaviors that allowed them to hunt a deer, or unexpectantly find a new stream of water, their NAC networks would have undergone surges of DA that would have allowed them to prioritize and repeat those successful behaviors in future similar circumstances more efficiently. With repetition and experience-induced refinement of striatal neural network interconnectivity, they would become increasingly motivated and skilled to perform actions that would result in more efficient delivery of survival-related resources.

LTD's role in weakening the strength of synapses as a part of learning may seem counterintuitive. Isn't loss of connectivity a kind of memory loss? Not exactly. LTD can be helpful when a part of a previous pattern of neural representation (or behavior) needs to be suppressed so that a new

behavior can be learned. For example, a baseball player that can only hit fastballs will need to figure out a different type of swing approach to hit a curveball. The player will need to suppress her automatic inclination to use her much-practiced fastball swing when she recognizes curveball conditions. This will help her develop a whole new curveball swing behavioral pattern with the help of both LTP and LTD in guiding what behavioral elements are most effective. Thus, the player will have increased the number of prepared behaviors available (fastball swing and curveball swing) for a wider variety of salient stimuli (looks of different pitches). Another way to think about the role of LTD is to consider that more information can be carried by a network (or an image) when there is plenty of contrast of firing pattern rates in the network or pixels in the image. (Note that a two-dimensional neural network, which can represent an image, is often called a "retina.") LTD thus also works in concert with LTP to help prevent learning from driving "white out conditions" in the network, in which case it would end up carrying very little information. In sum, DA signaling in the NAC is important for both LTP- and LTD-based neuroplasticity, so that salient stimuli and contexts that predict resource procurement are better acted on (by means of certain behavioral sequences) in future circumstances.

Note that in contrast to how DA neurotransmission is often described as representing pleasure, DA signaling in *the NAC is not all about feeling good, or experiencing hedonia, and so on* (here we go again with myth-busters!) It has been easy to overvalue and spread the "DA as feel-good-pleasure-transmitter" myth, based on the solid initial evidence that DA release happens in response to all these fun natural rewards (e.g., sex, food, winning!). But the reality is not this simple. In fact, as the four categories of salience listed above indicate, very negative, unpleasant, stressful, and painful stimuli or experiences, which are also salient, also provoke DA release into the NAC. Recognizing, remembering, and acting on key environmental information, whether it is "good" or "bad" news, pleasurable or painful, funny or stressful, is all potentially important for orienting and modifying motivated behavior for survival. If Mr. Caveman, while looking for delicious berries, came across bear claw marks and soon after narrowly avoided getting attacked by a bear, it would be advantageous to find, recognize, and act on similar tracks in the future so he could react appropriately.

So, it is not really accurate to understand DA as the pleasure transmitter, despite how it is often characterized in rudimentary neuroscience courses or pop psychology literature. Rather, as it functions in the ventral striatum, DA is more about orienting and changing motivation, across a range of emotional valences of different motivating stimuli. Indeed, complex emotions and states of pleasure versus suffering are not represented by the levels of any single neurotransmitter, or the activities of just a few neurons. Instead, these complex states are generated by very large interconnected neural networks of the brain that utilize many neurotransmitters, cell types and regions of the central nervous system (CNS) anatomy.

There are several clinical level observations that should be reviewed to help the reader understand that the identification of DA with pleasure is an oversimplified and largely misleading characterization: First, realize that one of the many neurobiological correlates of experiencing acute stress and/or pain – which are *usually* described as unpleasurable experiences – is the stimulation of DA release in the NAC. Either endogenous stress hormone release or the pharmacological delivery of corticosteroids can produce or correlate with higher levels of ventral striatal DA activity. In turn, heightened striatal DA activity can drive psychotic reactions (as a correlate of stress-induced psychosis in schizophrenia, for example), neither of which are generally considered as pleasurable states. Second, stressful events and pain can also trigger not just surges of psychiatric symptoms, but also relapses to drug use in people with addiction. And again, as shown in animal research, these states of stress often involve surges in DA influx akin to what priming (triggering) doses of addictive drugs can also generate. Third, neuroleptic medications, which all block striatal DA receptors to some extent, can constrain the flow of psychotic thought, altering motivation and motor behavior (e.g., via extrapyramidal side effects). However, these drugs are not actually very capable of extinguishing the ability to feel pleasure or experience reward, and they have little capacity to blunt drug highs or alter the course of drug addiction.

In realizing that either extreme of the stimuli-induced subjective state spectrum – pain or pleasure – may correspond to heightened levels of DA release into the NAC, it would seem to follow that novel stimuli or contexts in the middle of this spectrum, which may occur with uncertain emotional valence, could also cause elevated DA release as

well. And that is totally correct, as long as there is something new (**novel**), unknown, mysterious, or surprising about the stimuli or context. In this case the novel "thing" is perceived as having the potential to be either "good" or "bad" (or both), and the animal or person just has to further observe it, probe it, or experiment with it to find out more. As the marketing experts that hold such tremendous creative power in commercial advertising know, novelty can be, in and of itself, very motivating. Think of the "All New!" model of a "Brand New Car!" Indeed, excessive traits of **novelty-seeking** and/or **sensation-seeking** in humans and animals are associated with increased addiction risk in those individuals. And noncoincidentally, the use of an addictive drug in a novel environmental context has been shown to amplify the neurobiological and motivational effects of addictive drugs.

This neuroscience of salience, DA, and motivation also pertains to two other clinical-level phenomena that most of us are familiar with: (1) **humor** and (2) **sadomasochism**. By and large, humans want to (are motivated to) experience humor and laughter and the emotional correlate to this feeling is generally positive. We often pursue or strive to create humorous experiences (going to see a comedian; flipping through a funny vine online; creating jokes; acting silly). Although defining what makes something funny is tricky, and is not often the same for everyone, humorous stimuli or experiences are often salient (stand out to us) and yet have surprising, uncertain, or highly ambivalent or conflicted valence. Think of seeing a two-year-old wearing an old-man mask; or seeing a poodle dressed up as clown; or hearing a verbal pun with two meanings. Even the sound of laughter and the facial expressions and gestures that go with it seem to exist somewhere between joy and agony!

Then there is the activity of pulling a prank or jump scare on a friend, which gets us into the gray zone between humor and sadomasochism. In making pranks or jump scares, we find humor in watching the experience of another person when they encounter a highly salient and yet surprising, confusing, ambivalent, or unexpectedly bizarre experience. Going all the way over into **sadism** (which, unlike humor, can readily be pathological), people can experience pleasure, humor, and/or a gratifying sense of victory by delivering aggression, pain, punishment, and suffering to someone else. With **masochism**, people may experience a sense of pleasure, victory, or relief while also experiencing (or as brought on by) pain, punishment, and suffering. (Some psychiatric

illnesses, like borderline personality disorder, commonly show symptoms of self-injurious behavior which can generate a sense of gratification and relief in some patients, as a form of masochism.) In all these examples, the overarching point is that subjective emotional states generated by diverse salient stimuli (reward versus pain, pleasure versus suffering, known versus novel or surprising) are not represented by the same brain systems as motivation is, and none of these states have an exclusive connection to DA release into the NAC. Rather, DA neurotransmission is more about priming motivational circuits (e.g., the NAC network) for motivational attention and learning. This activity is important in the context of experiencing all kinds of different emotional states and environmental stimuli that are motivationally salient.

Downside of Salience Motivation

Unfortunately, our salience-informed motivation system can be problematic in environments of overabundance and other modern conditions that provide new ways and inputs to adversely manipulate ancient brain systems that involve DA neurotransmission. For ancient humans, and other mammals who evolved over millions of years in a time of relative resource scarcity and shorter natural lifespans, this system worked well to guide their learned behavior around obtaining things they needed while helping them avoid things that caused discomfort/harm. In our modern society, especially in technologically advanced countries, as epitomized by the United States, we have access to a myriad of not just varieties of food, but some of the saltiest, fattiest, most sugary food mankind has ever had available. More than this, we have access to unimaginably large volumes of instantly available novelty, literally at our fingertips with cell phones, internet videos, video games, and streaming television services. And of course, we have entire industries, legal and otherwise, that specialize on the mass production, sale, and circulation of large quantities of addictive substances, both new and old – including nicotine, alcohol, opioids, cocaine, amphetamines, cannabinoids, and so on, all of which enter the brain to induce DA release into the NAC.

It is a part of the normal human condition to feel at times like we are in a struggle for control of our many motivations. Many of us experience the challenges of controlling urges to overconsume sugary or fried foods, or to

buy stuff we don't necessarily need. Ever scrolled through social media so much that you risked running late to something important? Ever planned on just one more hour of television or video gaming in the evening before bed, only to end up going to bed two hours later? Often, urge conflicts such as these examples are not just one-time occurrences. They can also happen repeatedly, sometimes several times a month or even every few days, even as we regretted it the first, second, third ... and nth times around. Things can get a bit out of hand at least occasionally for most of us – even for the majority of us who are psychiatrically healthy and not addicted. In this way, our salience-informed motivation system, as guided by context- and stimuli-induced DA surges into the NAC, is not perfectly, logically, or optimally tuned at all times, to make us "go this way or that," or "do this or that," or keep us "doing this or stopping that and starting something else." The system operates a little bit **stochastically**, that is, it is enabled with some built-in *randomness, and capacity for inadvertent variation or flexibility.* So, sometimes with respect to natural reinforcers and motivations, we cut things a little short, and other times we take things too far. This jitter around the ideal stopping or change point for our behavior is actually often adaptive to, and reflective of, the real-world environment that we have to act in, which is actually always inconsistent, evolving – sometimes a little, sometimes a lot – so we are never confronted with *exactly* the same contexts or sets of competing motivations from one day to the next. The key is, we need a salience-informed motivation system that can, on the one hand, be highly flexible and adaptive to drastically changing environments. On the other hand, when circumstances are reliably the same as what we have experienced before, we need to be able to automatically, efficiently, and habitually do the same thing without us even having to think about it. Sometimes, compulsive behavior, occurring to the point where we can do very complex, goal-oriented behavioral sequences outside of conscious awareness (or independent of environmental change or feedback), is very adaptive.

This discussion brings us closer to understanding how drug addiction is actually quite closely related (neurobiologically and phenomenologically) to a host of nonsubstance-induced **impulse control disorders** (or nonchemical/**behavioral addictions** as they are often labeled), such as **pathological gambling, "sex addiction," excessive shopping, kleptomania, food consumption disorders**, and so on. It also helps us begin to frame what is happening in drug addiction in a highly

translational way (i.e., with an understanding that integrates our view of things both neurochemically and behaviorally). In the nonchemical addictions, diagnoses are made when certain behavioral patterns (often related to natural reinforcers, such as game winning, sex, food, and so on) are compulsively favored too much at the expense of the individual's other motivational priorities. In these conditions, individuals have extreme trouble with restraining their brain's motivational responses to the capacity of these natural (i.e., nonchemical) stimuli or contexts to invoke even mild DA surges. In the disease of drug addiction (which is much more common than the various behavioral addictions, yet can often be comorbid with them), the DA surge is artificially/pharmacologically induced at levels that are quite a bit higher, and perhaps more robustly sustained (as the drug use continues in a given using session). So, the capacity of these chemicals (nicotine, alcohol, opioids, cocaine, and so on) to drive a shift in incentive salience, neuroplasticity, and motivated behavior is all the greater, and more capable of driving the growth of a devastating, life-threatening addiction. Thus, in drug addiction, the salience-informed motivational system gets so relatively intensely and repeatedly activated pharmacologically that *habits can develop unintentionally* with very high efficiency (e.g., not really requiring that many repetitions of drug use). At the same time, this intense pharmacological DA activation can be particularly neurotoxic to the striatum's capacity to hold on to and represent other important motivational "codes" in the individual's **motivational-behavioral repertoire** that are not related to the actions of drug-seeking and drug-taking.

Neuroanatomy of Motivation and Addiction

Most complex actions, or behavioral programs, require various forms of sequencing, synchronization, and prioritization, with some degree of separation from thinking, emotion, or memory processing (that may or may not be related to the current behavioral program being executed). A person on a run must coordinate muscle movement in multiple limbs while keeping balance and remaining aware of their surroundings. While subconscious (lower brain) systems are busy regulating heart rate and blood pressure, higher cortical areas are engaged in listening to music or a podcast. At the same time, the individual may be feeling that recurring

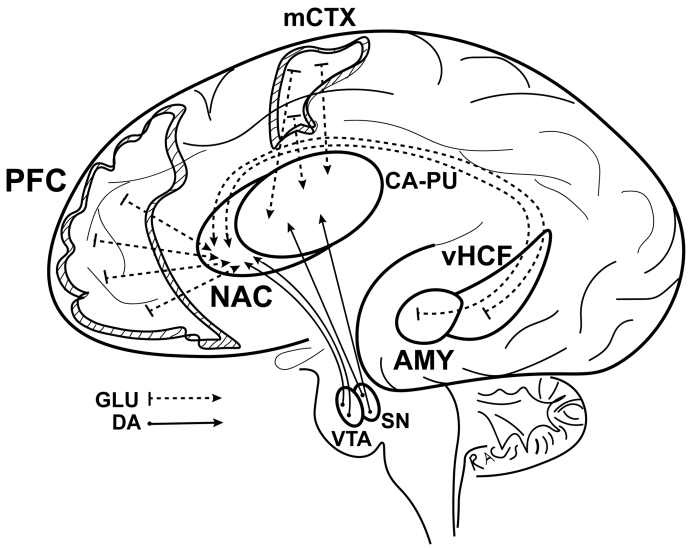

Figure 3.1 Neuroanatomy of motivational circuitry. Frontal cortical–striatal circuits involved in decision-making, motivational control, and motor programing. Ventral circuits governing decision-making and motivation include: PFC, prefrontal cortex; NAC, nucleus accumbens (i.e., ventral striatum); VTA, ventral tegmental area. Dorsal circuits governing motor programming include: mCTX, motor cortex; CA-PU, caudate–putamen (i.e., dorsal striatum); SN, substantia nigra. Key limbic inputs into the ventral circuit include: AMY, amygdala; and vHCF, hippocampal formation (specifically its ventral sector). Cortical–limbic axonal projections into the striatum convey information by glutamate (GLU) neurotransmission, whereas midbrain projections from the VTA and SN to the striatum convey signaling and modulate neuroplasticity via dopamine (DA) neurotransmission.

strain in their Achilles tendon while trying to modify their gait just a bit to avoid a bigger injury. They are aware of where they are going and how much longer they have to go. They may think about how the current run may help their training for the next mini-marathon, and how much of a longer run they want to do next time. Or they may be preoccupied the whole time with a deadline at work or the difficult interaction with a supervisor they had yesterday. The brain can accomplish all these tasks at the same time via **parallel processing**, where regions of the brain are simultaneously responsible for different types of information and tasks. But when these brain regions communicate with each other,

an individual can perform complex behavioral actions quickly and in an organized manner.

The **limbic system** of the brain is a distributed neurocircuitry (a large-scale neural network) of the central nervous system that houses and governs all the major high-level functions of the brain (e.g., personality, decision-making, emotion, motivation, short- and long-term memory storage, augmentation, recall, and so on). Within this anatomy, frontal–cortical–striatal circuits are responsible for generating, adapting, and implementing motivation (Figure 3.1). This **primary motivational circuitry**, which contains both cortical and subcortical compartments, uses both parallel and integrative processing to coordinate emotions, memories, bodily sensations, decision-making processes, and – ultimately – motivations to generate and drive behavioral programs. In the human brain, these circuits, along with our cortical-based powers of language and abstract cognition, have evolved to make our species the most powerful and capable of any living organisms in the known universe. But when these circuits are variously disordered, they give rise to various combinations of neuropsychiatric disorders and addictions.

While able to perform parallel processing, the distributed limbic circuitry is ultimately highly convergent upon the NAC (i.e., ventral striatum) region of the brain, which in coordination with the **prefrontal cortex (PFC)** acts a lot like the brain's equivalent of a computer's central processing unit (CPU). As introduced in Chapter 2, it is within the NAC where motivational processing principally occurs. Thus, the key distributed regions of the brain that inform what we are motivated to do (e.g., the PFC with its decision-making/encoding capabilities; the **hippocampal formation (HCF)**, with its short- and long-term contextual memory storage and recall capabilities; and the **amygdala (AMY)** with its emotional encoding capabilities) are all tied into the NAC by an anatomical convergence of **axons** (input fibers) from distant neurons across these regions that carry the neurotransmitter **glutamate (GLU)**. This convergence of inputs onto neurons within the NAC network is also coincident with DA-carrying axons from the midbrain's ventral tegmental area (VTA). Together, these convergent inputs allow for the integration of real-time cognitive, emotional, memory, and homeostatic (body-systems monitoring) information to generate and drive the flow of **motivational representations** (i.e., activity patterns across large neuronal ensembles) in the NAC. Then, after processing and packaging

this complex information, the NAC engages the dorsal striatum (**caudate putamen, CA-PU**) to help trigger, generate, organize, and execute sets of behavioral programs (complex motor sequences). In this way, the CPU-like function of the NAC digests the "input" components of motivation that originate from many parts of the limbic system. Then, based on this information, the NAC generates motivational representations that in turn facilitates changes in and guides the activity of the motor "output" stream, which involves the dorsal striatum (CA-PU) and the **motor cortex (MTC)**.

To compliment the more anatomically realistic depiction of limbic-motivational circuits shown in Figure 3.1, we provide a more functionally relevant map of information flow and integration that is happing through these same circuits in Figure 3.2. This neural network mapping, although grossly oversimplified, shows a big-picture view of the (1) "input" or "data gathering" streams that inform motivation (via primary and secondary sensory and limbic/homeostatic centers); (2) the CPU-like "data processing" unit structures where motivational codes are generated and processed (involving the PFC and the NAC); and (3) the "behavioral output" stream that generates observable sets of actions and behavioral programs.

Motivational Neurocircuitry: Central Processing Unit for the Brain's INPUT and OUTPUT Streams

The following outline compliments Figure 3.2 by providing a "big-picture" functional description of information processing and integration that occurs across these networks:

(1) ***Input: data gathering*. To form motivational representations (neural codes of neuronal firing patterns across NAC neurons that will help drive and organize behavior) the NAC network receives information about context, novelty, and salience, pertaining to current surroundings, emotional state, memory, bodily sensations, and systems.**

(a) *Primary and secondary sensory information (represented in the sensory cortices)* provide the homeostatic, emotional, memory, and decision-making centers with multimodal sensation (vision, hearing, smell, feel, and so on) contributing to a comprehensive, real-time representation of the individual's current situation.

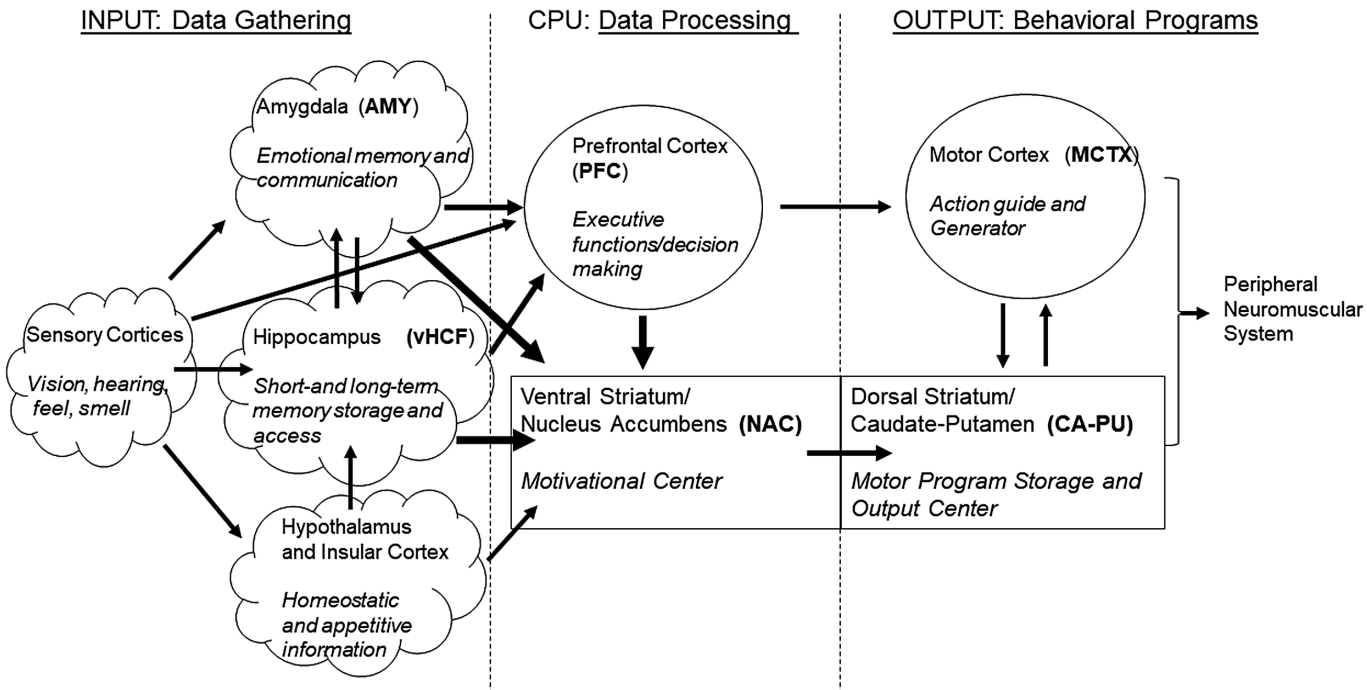

Figure 3.2 Information processing schematic of motivational neurocircuitry.

(b) The *amygdala* (AMY) interprets, processes, stores, and exports emotional information. This includes but is not limited to a wide array of multivalent social and threat information.

(c) The *hippocampus/hippocampal formation (HCF)* builds, stores, maintains, modifies, and exports complex short- and long-term memories. The hippocampus essentially stores maps and libraries of prior multimodal experiences and locations as tied to specific facts and or experiential details. Explicit memories require conscious recollection of experiences or facts.

(d) The *hypothalamus and insular cortex* monitor, represent, and help regulate a wide range of body homeostatic information including blood pressure, heart rate, urine output, body temperature, hormone balance, primitive appetitive status, alertness, and stress level (e.g., via the **hypothalamic–pituitary–adrenal (corticosteroid) axis**, and so on). The hypothalamus provides a CNS command hub for the control of body regulatory systems, operating automatically and largely unconsciously, whereas the **insular cortex** represents appetitive information that is accessible to conscious awareness.

Generally, primary sensory information and homeostatic information are packaged and integrated at the levels of the AMY, HCF, and ultimately the PFC, where they may (or may not) become integrated into conscious awareness (PFC) and motivational programming (NAC).

(2) ***CPU: data processing*. Glutamatergic axonal projections from the HCF and AMY converge onto both PFC and NAC networks to generate comprehensive "pictures" of the environmental/geographical, social, and emotional context, so that it may be thought about and/or responded to with behavioral actions.**

(a) The *prefrontal cortex (PFC)* is the ultimate stage of experiential processing and representation that essentially "makes the movie" that we are living in, in real time, that we are consciously aware of (and that we are able to store back into short- or long-term memory). The PFC, in communication with the NAC, is essential to the operations of attention, action selection, prioritization, and inhibition. The executive functioning of this part of the brain allows individuals to solve multistep problems, weigh pros versus cons, resist mental interference like background noise, split or focus attention to multiple tasks, and so on.

(b) The *nucleus accumbens (NAC)* is the key neural network and information-processing platform where information from the AMY, HCF, and PFC converge to gain access to downstream systems that generate and guide motivated behavior. The NAC (e.g., ventral striatum) along with the dorsal striatum generates, stores, and processes the neural codes that make up the motivational-behavioral repertoire of the individual. The NAC operates in the large functional space between the domains of (1) *thought-fantasy* (where complex "movies" of real-time experience can generate imaginary futures and action sets that are not actually acted out, primarily represented in the frontal cortex) and (2) *primitive–instinctual–reflexive–sensory–motor domains of action* (e.g., involving lower brain centers and the spinal cord), where forethought and learning are not required, and indeed may be detrimental, to producing behavioral action. So, on the one hand, information getting into the NAC from the PFC is information that is being "teed up" for driving actual behavior output. On the other hand, it is also information that is subject to complex multimodal sensory, contextual, emotional, memory, and high-order decision-making modulation and learning processes, which all occur on a much higher level than simple reflexes and instincts.

Generally, in the NAC, learned associations are formed between extremely large representation sets of complex multimodal contexts and potential action sets, where salience and past experiences (e.g., like complex "movie plots") are packaged into neural codes that are in turn exported to motor systems for the benefit of calling up or reorganizing complex behavioral programs (e.g., that facilitate the enactment of behavior within familiar versus new "movie plots").

(3) ***Output: behavioral programming*. CA-PU and motor cortices act out the behavioral programs as "directed" by the PFC–NAC system.** Once the behavioral plan has been "decided," motivational information from the NAC is relayed to the dorsal "behavioral" striatum so that complex motor programs can be carried out in a highly organized way. The dorsal striatum (CA-PU), also known as the **"extrapyramidal system,"** connects with, and guides the **pyramidal system** (i.e., the multisynaptic pathway from the **motor cortex (mCTX)** into the spinal cord, and then from motor neurons in the spinal tracts to the muscles) to generate complex motor actions. Note that the cerebellum is also involved, of course, in the

execution of complex motor actions, although its role in comparison to the CA-PU (and striatal assembly as a whole) is more tactical (how to efficiently execute) as opposed to strategic (why and when to execute). Also, it is important to understand that as the individual is enacting behavioral programs generated by the CA-PU network and creating changes and consequences in their body and/or the environment (as they are acting within it), they are also aware of and "recording" this behavior (and its results) in real time. Thus, the actions themselves and their consequences on the self and environment are being monitored and represented in the sensory stages as outlined above (1, **Input: data gathering**), to be recycled back into the motivational and behavioral computations happening in the NAC and CAPU.

Ventral versus Dorsal Cortical–Striatal Systems and Motivated Behavior

Cortical–striatal circuits can be understood as being organized as two major subsystems that have parallel anatomical design motifs that serve somewhat independent but highly interactional functional domains. As shown in Figure 3.3 the ventral system comprises a cortical region (the PFC), which projects glutamate (GLU) axons down into a striatal area (the ventral striatum/NAC), which also receives DA axons from a midbrain region (the ventral tegmental area (VTA)). In parallel, the dorsal system comprises another, more posterior–dorsal cortical region (the motor cortex), which also projects GLU axons into a striatal area (the dorsal striatum (CA-PU), which is more posterior–dorsal to the NAC), which also receives DA axons from a midbrain region (the substantia nigra (SN)).

The ventral system primarily generates and manages neural codes that control motivation (selection, prioritization, adaptation, and sequencing of motor programs) whereas the dorsal system primarily generates and manages the representations that control motor programs (complex behavioral output). Notably, many of the effects of the neural codes that are represented in the dorsal system are visible to outside observers as the enactment of the behavior sets. In contrast, the consequences of the neural codes represented in the ventral system are not directly observable, but can be inferred in terms of the prioritization, sequencing and organization of the behaviors that *are* directly manifest as the behavioral output product of

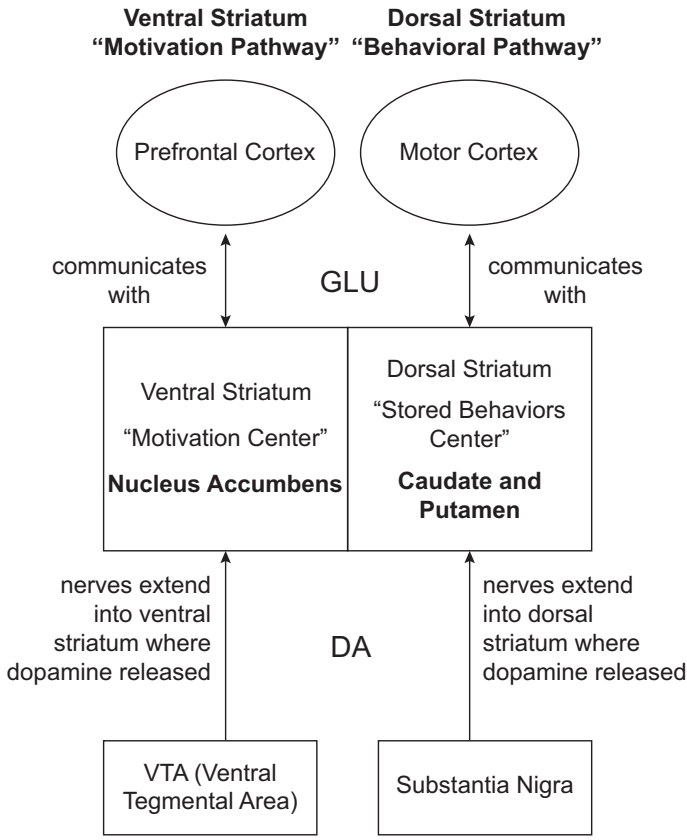

Figure 3.3 Ventral versus dorsal striatal circuits: motivational versus motor processing streams.

the dorsal system. Thus, we can infer what people are motivated to do by watching how they organize their behavior. In this way, the neural representations carried in the ventral system have a sort of hierarchical functional control over those of the dorsal system: motivation guides, organizes, configures, selects, prioritizes, and alters behavioral output. The way the ventral and dorsal striatal systems are anatomically interconnected (and to a significant extent overlapping, with no distinct territorial boundary) to allow this kind of hierarchical control of motivated behavior has been described in considerable detail by Haber and colleagues, as a kind of polysynaptic, spiraling flow of information through cortical–striatal subcircuits along a ventral–anterior to dorsal–

posterior gradient. Along this gradient, cortical inputs to the striatum become gradually less involved in planning and more involved with execution of behavioral programs. Similarly, midbrain dopamine inputs to the striatum gradually become less involved with the generation and flow of motivational representations and more involved with the flow of concrete behavioral output.

The striatal component of the dorsal system (i.e., the CA-PU) is a large neural network that operates as a kind of library of learned, habitual behavioral programs (or rather, the neural firing pattern representations that encode for behavioral action sequences). In this way, the CA-PU is a final output station of motivated behavior. Because of its anatomical position, its internal network design, and given its functional role within the cortical–striatal assembly, the CA-PU provides tremendous computational advantages to the brain (and the individual's survival) that relates to its capacity to store and execute a vast library of neural firing pattern representation sequences. In effect, the CA-PU is able to play out any one of a huge number of firing pattern sequences (like a library of thousands of different movie subplots in which the individual is the principal actor!). This capacity allows the individual to (a) avoid having to relearn very complex sets of motor sequences (e.g., every time they are needed) and (b) perform complex motor programs without requiring intensive PFC input and demand, which allows the PFC to do all kinds of other things (like thinking, imagining, remembering, or planning about other things or future events) while the striatum is "autonomously" enacting complex behavioral programs in the present. This capability has been an immensely successful feature of mammalian brains, giving us great computational efficiency needed for mapping and modifying extremely complex behavioral repertoires onto the extremely complex, changing environments we live in.

Plasticity, Learning, and Adaptation of Motivated Behavior

Again, even with all this awesome capacity to store and semi-autonomously execute habitual (well-learned) motor programs, the CA-PU still needs guidance on how to prioritize, sequence, alter, and enact these motor programs with the best timing. As we have already reviewed, this is where the NAC and its motivational encoding comes into play. But there is much more to this story because things are always changing in the real world: First, the individual is growing and aging through different

stages of developmentally appropriate cognitive-behavioral skill sets and motivational priorities. Second, the environment itself is drastically evolving though the seasons and a wide range of many other natural and social events and epochs. So, the motivational-behavioral repertoire of the individual must change as well.

In order for motivated behavior to change, to allow the individual to best adapt to their changing bodies and the changing environment, the information storage and processing within cortical–striatal circuits must change. This ultimately means, on the brain-cellular level, that the neural connectivity and transmission of firing pattern activity within and across cortical–striatal neural networks much change. This is where DA, again, comes in.

Pathological Changes in Structure and Function

Dopamine and Motivational-Behavioral Repertoires

At the start of this chapter we reviewed how DA signaling in the NAC serves a *short-term function* of alerting the neural network to any one of a number of classes of motivationally salient stimuli or events. An additional, somewhat related but distinct immediate function of DA release that is most clearly tied to its function in the CA-PU is to facilitate initiations of, transitions between, and overall flow of specific motor actions within larger behavioral programs. So, when DA levels are pathologically decreased (as with the loss of SN neurons that project DA-bearing axons into the CA-PU; Figure 3.3), the brain becomes hampered and incoherent in its ability to internally communicate desired motor instructions and complex movements. This produces the core symptoms of **Parkinson's disease** including bradykinesia, resting tremor, muscle rigidity, apparent apathy of facial expression, and slowness to initiate or transition between behaviors.

In addition to these immediate functions, *DA also has a long-term function* in the striatum of facilitating neuroplasticity, as we have also introduced earlier in this chapter. Coming full circle with this understanding of DA as a "learning signal" in the striatum, in light of our prior description of the NAC and CA-PU as key centers for motivational encoding and behavioral programming, we can now understand that DA is

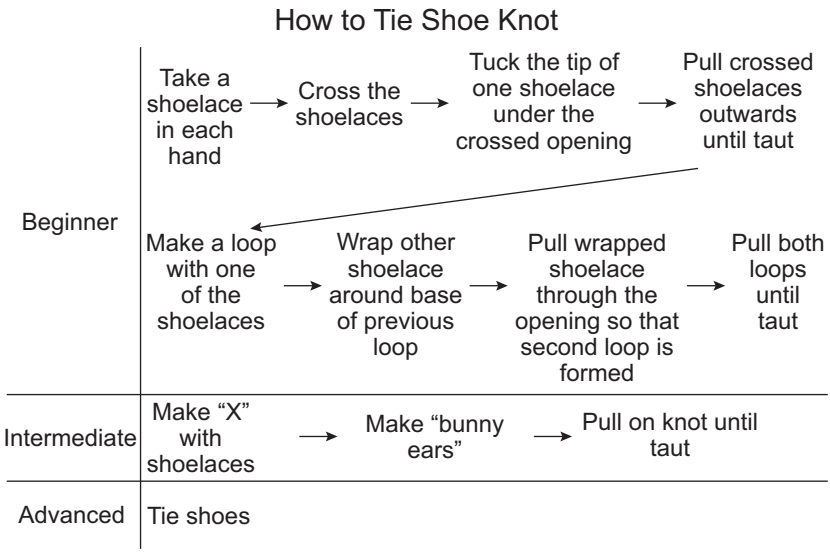

Figure 3.4 Acquisition of automated behavioral sequences. Motivational learning incorporates habit formation as a key mechanism for growth and adaptation of the motivational-behavioral repertoire.

also critically involved in longer-term changes in both motivation and habit formation.

Over time, as the individual experiments with and acquires new skills, DA neurotransmission in the NAC helps direct and maintain motivation (effort) to efficiently acquire and master those skills that are most important for survival. Simultaneously, in the CA-PU, DA efflux supports neuroplasticity that produces increasing efficiency in executing "desired" motor programs. For example, consider Figure 3.4, which illustrates a child's mastery of tying a shoe. Clearly, for children under six years old, this is a very desirable behavior to acquire. After all, they want to seem accomplished on this key task in front of their friends and parents! And, who wants to waste time "waiting for mom to tie my shoe"? Also, children know it is best to have shoes tied at all times to avoid tripping! So, in the NAC, as facilitated by DA efflux, the novelty of learning and progress in mastery reinforces the child's motivation to practice trying their shoe. At the same time, as they progress from Beginner to Intermediate to Advanced, the act of tying one's shoe seems to happen like a coalescence of initially complex component action parts or steps. At first, each step

takes some time and requires the integrated contribution of a broader array of frontal–cortical, motor, and sensory cortical areas. But with practice, as facilitated by DA-mediated neuroplasticity, the CA-PU learns to put the motor actions (neural firing pattern sequences) together, with less and less cortical input over time, until finally, tying a shoe seems to happen as one seamless, quick, and beautiful action, automatically, without thought, and hardly making it into conscious awareness or memory of the day. The kid can soon even tie their shoe while still watching television before going to school!

We are all equipped with thousands of skills (i.e., complex behavioral sequences) that we have acquired over the years. This accumulation of behavioral programs is not merely adaptive simply because it allows us to do a lot of things. It is also highly adaptive because our motivation system, anchored on the NAC and the neurotransmission of DA into the NAC, reinforces practice of desired behaviors, maintains adaptive prioritization and sequencing of long strings of behavioral sets, and allows for the formation of new sets and sequences of behaviors.

In effect, **the motivational-behavioral repertoire** of the individual that is generated and maintained by the cortical–striatal assembly is like a very large representational map of motivational links (represented in the NAC as neural codes) that interconnect behavioral nodes (i.e., specific behavioral programs, represented in the CA-PU as neural codes). The large collection of behavioral programs we perform (as encoded by the CA-PU), and the multiplicity of sequences or pathways (as encoded by the NAC, which configures CA-PU activity) by which we can act out the behavioral programs, makes up a very large representational map stored in our brains. At all times, as long as we are alive, we are doing something that is somewhere on this representational map and heading somewhere else on this representational map! And the better this map matches with and is able to adapt to the survival-dependent features of the real, ever-changing environment, the better it is for the survival of the individual and their species.

What we are describing here is a **neuroinformatic** level of information processing in the brain. Neuronal assemblies make up neural networks that represent informational codes. These informational codes, existing on the neuroinformatic level, are made up of evolving firing pattern representations distributed over large populations of interconnected neurons. These codes *represent* environmental reality in the **(1) Input: data gathering** stream.

Then they are acted on and transformed in the **(2) CPU: data processing** stream. Finally, they are repackaged and presented to the **(3) Output: behavioral programming** stream, which encodes and plays out our complex motor actions sequences.

It turns out that in the natural world, maps of links and nodes (that are biologically based, wherever they may be found) are inherently functionally stronger and more developmentally efficient if they follow (and grow by) a **"scale-free" structural motif**, where a minority of nodes are highly interlinked with many others, but the majority of nodes have relatively few links with other nodes. As described in Chambers et al. (2007), behavioral evidence suggests that motivational-behavioral repertoires of humans and other animals (which exist in the brain on the neuroinformatic level) tend to develop from childhood through adulthood following a scale-free design motif (Figure 3.5). In this neuroinformatic organization (or mapping), motivational codes (represented in the NAC network) form the links that interconnect behavioral codes (represented in the CA-PU network). In this way, highly desirable (i.e., highly adaptive) behavioral programs become more highly connected hubs in the motivational-behavioral repertoire. Also, highly desirable, useful, and often repeated sequences of certain behaviors can become more invariably linked into a longer, more efficient, and more automatically executable sequence (as in habit formation). DA activity in the NAC, via both its motivational-salience alerting and neuroplasticity facilitating effects, thus plays a key role in maintaining NAC neural network capacity to achieve the most optimal overall hierarchical structuring of our motivational-behavioral repertoires. So, in mediating the tension between network plasticity versus network connection stability in the NAC, DA has a hand in flexibly remodeling, shrinking, and growing the motivational-behavioral repertoire while allowing it to maintain and form highly stable automatic behavioral sequences in the face of ongoing environmental changes and challenges.

Sensitization and Habit formation in Cortical–Striatal Networks

As covered at the end of Chapter 2, addictive drugs of all varieties, regardless of their differential intoxicating profiles, share a capacity to in some way pharmacologically invoke DA release into the NAC. It is this

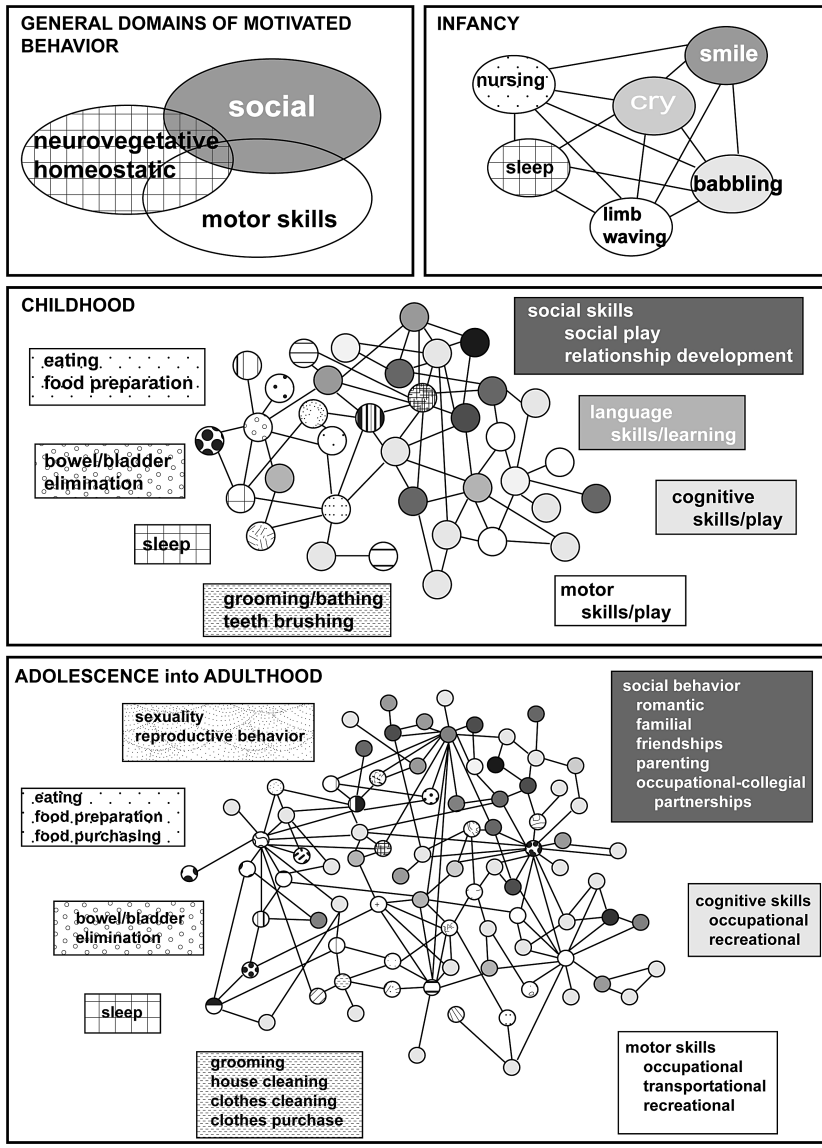

Figure 3.5 Structure and neurodevelopment of the motivational-behavioral repertoire.

pharmacological effect that is most directly linked to the addictive effects of these drugs. Based on the additional knowledge we have just reviewed, we can now begin to understand how substance-induced provocation of

DA neurotransmission facilities this addiction-generating effect by reorganizing neural network connectivity in the striatum, which in turn creates a reorganization of the motivational-behavioral repertoire. This process has been likened to a sort of "hijacking" of natural brain mechanisms that provide hierarchical control and adaptation of complex behavior, especially with respect to habit formation.

Naturally, DA transmission in the ventral striatum facilitates the formation of increasingly automatic and efficiently performed strings of behavioral sequences. Conditions are particularly ripe for this process when the behavioral sequence being formed is motivationally well reinforced (i.e., such that the individual is motivated to frequently practice it) and when it is highly adaptive (e.g., yields resources for the individual or their group). At first, when the behavioral sequence is being acquired and learned (and being appropriately linked to other behavioral programs in the individual's motivational-behavioral repertoire) there is a significant amount of extrastriatal brain region involvement in the process. While the ventral and dorsal striatum are learning together how to more efficiently, and interactively execute particular neuronal firing pattern sequences within their respective neural networks, the neocortical–limbic inputs to the ventral striatum (e.g., including the PFC, AMY, HCF, and other regions) are quite actively engaged in contributing to ventral striatal firing pattern generation (and modification of these patterns). In this way, these distributed limbic regions are helping to teach the ventral striatum how to organize and prioritize behavioral sequences that the dorsal striatum is also learning to execute with greater efficiency. DA neurotransmission into the NAC/ventral striatum, which is provoked when the individual encounters motivationally salient stimuli (which should in turn drive certain behavioral programs), heightens the ability of PFC, AMY, and HCF inputs to the ventral striatum to drive neuroplastic change. Thus, these inputs sort of help "teach" the NAC network to acquire firing pattern representations (and sequences of those representations) that more efficiently and autonomously drive behavioral program sequences that are executed by the dorsal striatum. DA neurotransmission in effect facilitates the principal mechanisms of neuroplastic changes (LTP and LTD) that are occurring at the synaptic interfaces of both cortical–limbic inputs into the ventral striatal network and the neuronal interconnectivity within the neostriatal network. Over time, as a complex behavioral

sequence is executed more efficiently and automatically (as guided by DA release in the ventral striatum), "unnecessary" or "unproductive" behavioral fragments, motor errors, and *decision points* are cut out of all the steps in the sequence as much as possible. At the same time during this process, PFC, AMY, and HCF–limbic inputs to the ventral striatum are needed much less, and the individual is able to instigate and perform quite complex sequences of behaviors fairly automatically, with relatively minimal energy and computational costs to the brain as a whole.

In this way, DA neurotransmission (especially as artificially provoked by addictive drugs) has a key role in allowing both habit formation and sensitization, which the reader may now understand are closely related phenomena. In **habit formation**, a complex behavioral sequence is performed more efficiently, invariably, and autonomously, even to the point of being enacted compulsively. In sensitization (which essentially makes the habit more compulsive), the motivation to enact the habitual behavioral sequence is increased over time relative to other motivations that might normally drive the performance of other behaviors. Along with this increasing prioritization of motivation "#24" (as represented by a certain neural firing pattern across the ventral striatal/NAC neural network) to perform behavioral sequence "X,Y" (as represented by a neural firing pattern sequence across the dorsal striatal/CA-PU network), there is also a strengthening of the capacity of environmental stimuli and experiences (i.e., triggers) to cause motivation #24 (as represented in the NAC network, which leads to behavior X,Y) to emerge. So, over time, with greater sensitization, there is an increase in "motivational" linkages that lead from different environmental contexts and behavioral sets that the individual may be engaged in to the habitual (e.g., drug seeking/using) behavioral sequence X,Y. As this growth process happens, behavioral sequence X,Y becomes a much more highly connected hub (of the motivational behavioral repertoire), and the behavioral sequence it represents (drug-seeking/-using) is executed with greater frequency. In either case, with both habit formation and sensitization, there is an active change and growth process involving the structure of motivated behavior, where motivations (#24, #129, #17, . . .) that interlink specific behavioral programs (B, Q, H, D, X, Y, . . .) are revised and restructured. When operating under normal conditions in a healthy brain, this ongoing

restructuring (or maintenance of the structure) tends to keep the **motivational-behavioral repertoire** (that is encoded and stored by neostriatal firing patterns) optimized (well mapped) to the external world the individual is living and acting in. In the addiction process, the DA signal that is generated by the drug is artificially (but powerfully and specifically) reinforcing drug-seeking and drug-taking (e.g., X,Y) behavior as highly connected nodes in the motivational-behavioral repertoire.

Molecular and Cellular Events Underpinning Motivational Plasticity and Addiction

Up to now, we have discussed the pathological growth process underlying addiction on three interactive levels including:

(1) *The clinical-behavioral level*: Where addiction is observed as a pathological–involuntary growth of motivation to seek and use an addictive drug at the expense of other (healthy motivations) and despite damaging consequences.

(2) *The pharmacological–neurochemical level*: Where addictive drug use invokes pathological surges of DA neurotransmission within the ventral striatum (NAC) that accumulate to produce increasingly abnormal neuroplasticity and learning effects pertaining to motivation.

(4) *The network–neuroinformatic level*: Where accumulating alterations in motivational representations (firing patterns across neuronal ensembles) in the NAC network has implications for altering and reorganizing the flow of motor program representations (devoted to drug-seeking and use) generated in the dorsal striatal network.

(3) *Molecular/Cellular*

With these three levels of understanding of the disease process, we are approaching a more complete picture of the vicious cycle of addiction as an autonomously reinforcing interplay between biology and behavior that grows larger and out of control in a snow-balling effect. But there is still one more level we need to discuss that is intermediate between the (2) *pharmacological/neurochemical* and the (4) *neuroinformatic* levels. Hence, the reader will notice that in the list above, we have deliberately omitted a level 3, which we will introduce now, last, but not least, as the *molecular and cellular level*.

The body of basic neuroscience research that has characterized the molecular and cellular pathophysiology of addiction (much of it only emerging in the last 25 years) is very large and has been contributed to by scores of labs and thousands of people around the world. For the purposes of this book, we can only afford to summarize this literature in the broadest of strokes, and in the most accessible way, leaving many details and mentions of specific discoveries and scientists out of focus.

The question we have left to answer is: How, and through what brain substrates, do the pathological effects of drug-induced DA transmission in the NAC translate to the neuroinformatic levels where the motivational-behavioral repertoire of the individual is encoded and structured? The answer to this is where the molecular and cellular neuroscience of addiction takes center stage. Interweaving a bit of history and science here provides a good approach to describing this level.

For the last 30 or so years, medical students have been required to memorize (if only briefly) the basic molecular chain of events that underpin **cell signaling and response**. This chain can be summarized as follows: A chemical stimulus lands on receptors sitting on the external face of the cell membrane, which initiates a cascade of protein interactions inside the cell cytoplasm that eventually reach inside the nucleus of the cell. This, of course, is the famous **G-protein–coupled receptor cascade**, which is so widely taught to students of medicine, pharmacology, and cellular physiology because it is so universal. G-protein–coupled receptor systems are widely relevant across many different life forms, body organs, and diseases processes. *They enact a basic molecular mechanism by which cells inside the organism can react to their local environments to change their phenotypes.* As chemical stimulus X increases in concentration in the environment of the cell, the G-protein–coupled receptor notices this change. This produces a chain reaction across a cast of characters inside the cell (e.g., **adenylate cyclase, cyclic-AMP**, and others), which eventually impacts protein coverings on the DNA, access to the DNA, and the transcription machinery of the DNA. So, DNA expression changes, especially with sustained stimulation of certain G-protein–coupled receptor pathways. Then, with DNA expression changes, the cell experiences wholesale changes in the types and proportions of structural and functional proteins that are being produced. Thus, the function and form of the cell itself can be totally altered, and, if enough DNA expression

changes occur in a sustained way, the phenotype of the cell itself begins to change, potentially in a semipermanent way.

An important neuroscientific advance was the realization that G-protein–coupled receptors existed not just throughout the body but all over the brain, involving many different neuronal cell types and neurotransmitter receptor systems. Identifying these receptor systems, how they may be triggered by specific neurotransmitters, and elucidating their specific effects in certain brain regions was then recognized as a way to understand how certain neurochemical stimuli could change neuronal phenotypes (which is a sign of *neuroplasticity*). In the early 1990s, Eric Nestler, David Self, and colleagues helped pioneer the science that established that – via G-protein–coupled receptors – addictive drugs exert neuroplastic effects on brain systems involved in addiction, and that these changes produced behavioral changes in animals consistent with addiction. This work included demonstrations that G-protein–coupled receptors are involved in the generation of opioid tolerance and withdrawal syndromes via **norepinephrine/alpha adrenergic receptors** in the **locus coeruleus**. But more on target to the general process of addiction pathogenesis, they also showed that addictive drugs, working via DA receptor systems (which were also G-protein–coupled) in the NAC also changed neuronal DNA expression in those neurons. As those neurons were involved in representing the brain's motivational encoding, it was clear that some of the key molecular underpinnings of pathological motivational change in addiction had been described. Within the decade, a number of short- and longer-term molecular factors inside NAC neurons had been found to be involved in the post-DNA translational landscape of addictive drug exposure.

Soon, these molecular changes were linked to changes in functional markers of learning and memory involving NAC neurons (e.g., see prior discussion of LTP/LTD mediated by DA neurotransmission). And even more concretely, by the turn of this new century, as demonstrated by Robinson and Kolb, it was possible to see the phenotypic changes in NAC neurons brought on by addictive drugs under a microscope. Chronic exposure to several addictive drugs, first including cocaine and amphetamines, but then other types including nicotine and opioids, was shown to literally change the **dendritic structures** (neuronal branches) and the shapes and numbers of synaptic spines on NAC neurons (which receive signals from incoming axons from other

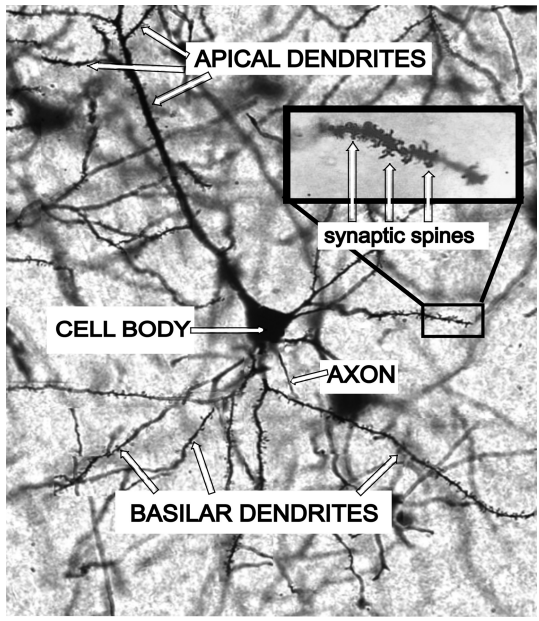

Figure 3.6 Microanatomy of a typical PFC neuron. This micrograph shows the morphology of a main PFC neuron (a "pyramidal" neuron named for the pyramidal shape of the cell body), revealed by Golgi staining of rat cortex. Apical and basilar dendritic tree branches receive incoming signals from distant neurons that send axonal projections interfacing at the synaptic spines (rich in receptors). A complex neurochemical (and yet quite mathematical) summation of excitatory (GLU), inhibitory (GABA), and modulatory (e.g., DA) neurotransmission at the synaptic spines and across the dendritic branches of the neuron determines the rates of action potential generation (a sharp spike in electrical activity) that gathers at the cell body and propagates down the axon to a distant neuronal target. It is likely that the axon shown here projects down into the NAC, where it may signal to a medium spiny neuron that helps store and represent motivational information.

neurons). Some compelling details of this science also included documented differences in these morphological effects depending on if (a) the animals were self-administering the drugs versus having the drugs delivered passively, or (b) whether the animals were experiencing the chronic drug exposures in novel versus familiar environments. To top it off, these kinds of addictive drug effects were not anatomically limited to the NAC but were also present in various degrees in PFC regions involved in decision-making and impulse control (Figure 3.6). Thus, by 2005

a fairly complete "bottom to top" description of the multilevel pathophysiology of addiction – spanning from molecular to cellular to neuroplasticity to changes in brain region function to changes in motivated behavior – had been described. To this day, there is still no type of psychiatric illness other than addiction for which the disease mechanism is so relatively well understood and elegantly characterized within and across all these levels. As we will describe in the next chapter, this focus on addiction as a drug-induced pathology of the neuroplasticity of motivation has important implications for our understanding of addiction as both a neurodevelopmental disease and as a disease that is fundamentally interconnected with and worsened by mental illness.

Putting It All Together: Addiction as Acceleration of a Vicious Brain-Behavioral Cycle

Equipped with the **systems neuroscience** understanding of motivation covered in this chapter, it is possible to construct a fairly clear and succinct summary of what is happening in the pathogenesis of addiction. As we will cover in more detail in Chapter 4, different individuals have different biological set points (or degrees of addiction disease risk). Essentially, however, the disease advances in a similar way across all individuals, albeit differing by how quickly or how many doses (of the drug) are required to get the disease process underway.

We have characterized the addiction disease process as an abnormal growth process (i.e., involving growth of motivation to seek and use a drug), but it is also helpful to think of it as a train leaving the station, gaining speed as it accelerates down the tracks, with the speed of the rotation of the wheels growing in proportion to the acceleration of the disease process itself. In this analogy, it is also helpful to think of the four levels of addiction pathogenesis introduced above as representing four points on a rotating locomotive wheel (Figure 3.7). Note that the

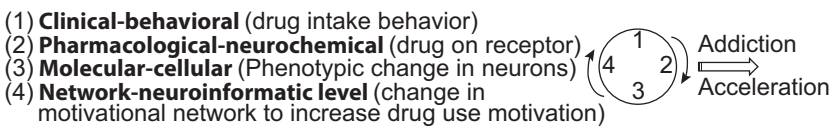

Figure 3.7 Vicious four-part cycle of addiction acceleration.

information processing by striatal neural networks on level 4, the neuroinformatic level, is what generates the behaviors (and their sequences) observable on level 1, the clinical behavioral level. So, events occurring on levels 1 (drug-use behavior), 2, 3 and 4 (brain changes to increase motivation to use) cycle back to increase the growth of behavior occurring at level 1 (drug use) – creating a vicious, positive feedback cycle that accelerates the individual into addiction.

At first the train is standing still, but as heat energy is initially applied to the hydraulic pistons, there is an impulse that is transmitted to the wheels to get the train moving, however slowly. By analogy, we can think of that first-time use of an addictive drug by the individual producing a large DA release in the NAC/ventral striatum – kind of like the beginning of energizing the propulsion system of the locomotive. But the locomotive is heavy and so only a sustained supply of energy to the propulsion system can really get it moving. Similarly, that initial drug-induced DA efflux that was produced by and paired with the act of taking the drug for the first time does not produce much of a significant neuroplastic effect. The effect is relatively small and incremental, and all by itself not likely to change motivation in a major way. Nevertheless, the effect is there, and it can be understood as producing some (slight) increase in the motivation (and probability) for using the drug again. This growth in probability of using again means that the waiting time until the second use, should such an event occur, will likely be much shorter. For example, if an 18-year-old uses cocaine for the first time, it will likely be much sooner than 18 more years before the second use, if they use again. The incremental neuroplastic effects of that first episode of drug use have also slightly sensitized the context that the individual was in, when they used the first time, as something that could subsequently, more powerfully, instigate the motivation (and behavior) to use the drug again. The compounding growth of both of these probabilities makes it more likely that for a given individual, the drug will be used again, and soon. Said another way, across a group of individuals, the likelihood that some fraction of them will use again, and soon, is all but certain.

Now, for those people who do use again, for example, within the same week of the first use: they have fairly quickly repeated two rotations of the four-part cycle from behavior to brain and back to behavior again. And this time the incremental increase in the motivation to use the drug compounds with the prior incremental increase that the first drug use

initially produced. So, after the second use, the net motivation to use the drug is even greater than after the first time, which again leads to more increased probability that the individual will use sooner, leading to the taking of third and fourth doses, with even shorter time gaps in between doses. Hence, returning to the train analogy, the train is now building speed and momentum, requiring less energy to keep it moving, but at the same time requiring much more opposing energy to get it stopped.

In this accelerated growth process, drug-seeking and drug use become linked to and increasingly intercalated within already existing pathways within the motivational-behavioral repertoire of the individual. This can be readily observed, for example, with the changes in motivated behavior that happen with the admixture of automobile driving and the progression of nicotine addiction (Figure 3.8). Eventually, the act of lighting up for the drive home after work is automatically triggered by the act of getting into the car, and the act of smoking becomes one with the processes of driving itself.

More generally, the addiction diseases process can be understood on the neuroinformatic level (as produced by cellular and neural network changes) in terms of its progressive impact in the motivational-behavioral repertoire as the installment of a drug-taking behavioral program (a node

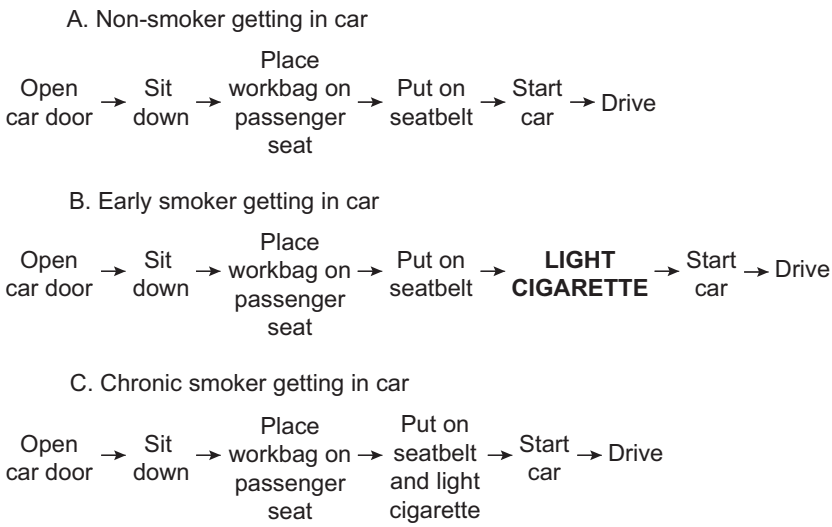

Figure 3.8 Incorporation of addictive behavior in a behavioral sequence.

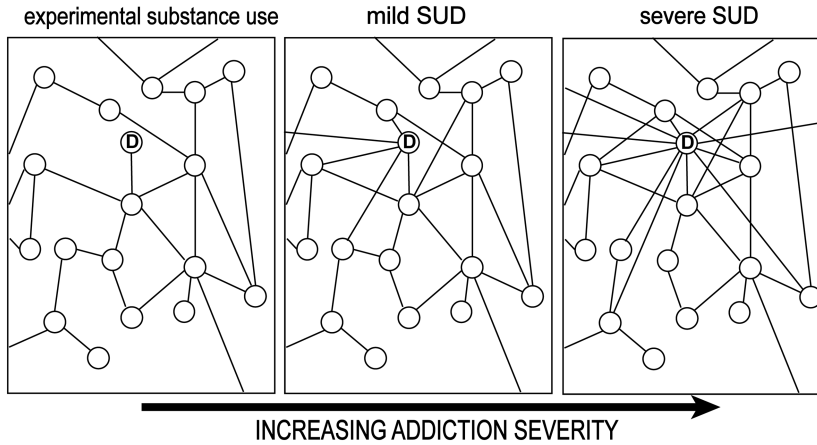

Figure 3.9 Growth of addiction disease as a progressive restructuring of the motivational-behavioral repertoire. Drug-taking behavior introduced as experimental use in the motivational-behavioral repertoire (left panel; node "D") becomes more highly connected with other behavioral nodes and motivational pathways from early addiction (middle panel; mild SUD) to late, severe stages (right panel; severe SUD). The restructuring of motivational pathways around the drug-taking node is facilitated by pathological, DA-medicated neuroplasticity with PFC–NAC (ventral striatal) circuits, creating increasingly locked-in motor sequences that favor drug acquisition and use behavioral programs represented in CAPU (dorsal striatal circuits).

in a local domain of the motor program network of the motivational-behavioral repertoire as illustrated generally in Figure 3.5). With illness progression, motivational links (which link one behavioral program to the next) that normally allow for the prioritization and sequencing of larger, more complex behavioral sets begin to accumulate around the drug-taking behavioral node, attaching that activity to other behaviors and domains of behavioral sets (Figure 3.9). In this way, many other behaviors and contexts (in which other behavioral sets normally happen) become "triggers" for craving (urge to use), leading the person toward drug use. At the same time, healthy motivations and behaviors (socializing with friends, driving a car) can also become incorporated into the act of drug-seeking and procurement, which eventually leads to the drug-use behavioral node. This change in the motivational-behavioral repertoire not only summates into a greater likelihood and frequency of

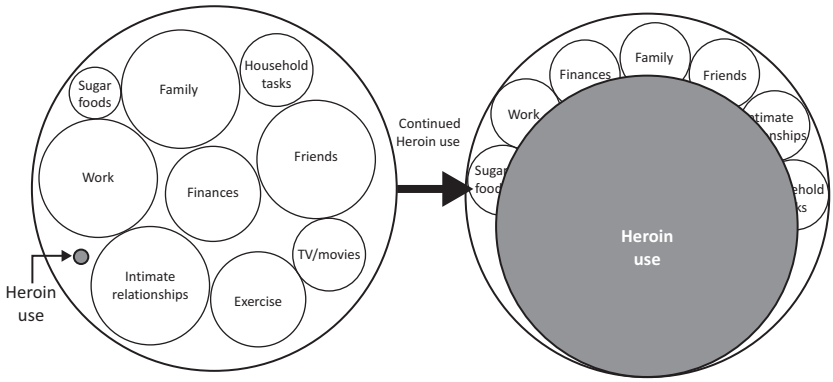

Figure 3.10 Pathological growth of addictive behavior: a motivational tumor within the motivational-behavioral repertoire.

drug use (and the growth and co-opting of many activities to achieve drug access), but also comes at a collateral cost. Other healthy motivational links and behavioral nodes (not incorporated into drug-seeking and drug-taking) are enacted much less frequently and can become isolated, dismantled, extinguished, or destroyed (Figure 3.10).

As we have reviewed in prior sections of this book, addiction-related changes to the motivational-behavioral repertoire are not really produced by the intoxicating profile (and biology) of a given substance. In addiction, a quite similar process happens across different addictive drug types, whether the intoxication profile of the drug is as an upper or a downer or is heavily impairing or sparing of cognitive function. For nicotine, as illustrated in Figure 3.8, the addiction grows initially in a relatively harmless way in terms of its overall effects on the motivational-behavioral repertoire, because nicotine does not really have any major intoxicating–impairing effects (which could quickly rub out or preclude the performance of other activities). But for heroin, a highly intoxicating opioid that is on par with nicotine's addictive strength, the growth in drug use and seeking quickly becomes devastating to many subregions of the individual's motivational behavioral repertoire (Figure 3.10). This is where the runaway train of addiction has become like a tumor, compressing, incorporating, or destroying many other domains of the individual's free will and occupational and social function, sometimes going so far as subsuming

or sacrificing the patient's natural motivation to stay alive. In this way, addiction grows like a cancer within the motivational-behavioral repertoire, accelerating into a nonstop cycle of constant drug pursuit and motivational enslavement, dedicated to more drug use despite all manner of psychiatric, medical, and social consequences.

BIBLIOGRAPHY

Bechara, A., H. Damasio, H. R. Damasio, and G. P. Lee. 1999. Different contributions of the human amygdala and ventromedial prefrontal cortex to decision-making. *J Neurosci*, 19: 5473–81.

Bernstein, H. G., H. Dobrowolny, B. Bogerts, G. Keilhoff, and J. Steiner. 2019. The hypothalamus and neuropsychiatric disorders: Psychiatry meets microscopy. *Cell Tissue Res*, 375: 243–58.

Berridge, K. C., and T. E. Robinson. 1998. What is the role of dopamine in reward: Hedonic impact, reward learning, or incentive salience? *Brain Res Rev*, 28: 309–69.

Centonze, D., B. Picconi, P. Gubellini, G. Bernardi, and P. Calabresi. 2001. Dopaminergic control of synaptic plasticity in the dorsal striatum. *Eur J Neurosci*, 13: 1071–77.

Chambers, R. A., W. K. Bickel, and M. N. Potenza. 2007. A scale-free systems theory of motivation and addiction. *Neurosci Biobehav Rev*, 31: 1017–45.

Chandola, T., J. Head, and M. Bartley. 2004. Socio-demographic predictors of quitting smoking: How important are household factors? *Addiction*, 99: 770–77.

Charney, D. S., J. D. Buxbaum, P. Sklar, and E. J. Nestler (eds.). 2013. *Neurobiology of Mental Illness*. New York: Oxford University Press.

Cummings, J. L. 1993. Frontal–subcortical circuits and human behavior. *Arch Neurol*, 50: 873–80.

Graybiel, A. M. 1995. Building action repertoires: Memory and learning functions of the basal ganglia. *Curr Opin Neurobiol*, 5: 733–41.

Graybiel, A M. 1998. The basal ganglia and chunking of action repertoires. *Neurobiol Learn Mem*, 70: 119–36.

Green, R., A. Clark, W. Hickey, J. Hutsler, and M. Gazzaniga. 1999. Braincutting for psychiatrists: The time is ripe. *J Neuropsychiatry Clin Neurosci*, 11: 301–06.

Groenewegen, H. J., C. I. Wright, and H. B. M. Uylings. 1997. The anatomical relationships of the prefrontal cortex with limbic structures and the basal ganglia. *J Psychopharmacol*, 11: 99–106.

Gruber, A. J., G. G. Calhoon, I. Shusterman, G. Schoenbaum, M. R. Roesch, and P. O'Donnell. 2010. More is less: A disinhibited prefrontal cortex impairs cognitive flexibility. *J Neurosci*, 30: 17102–10.

Haber, S. N., J. L. Fudge, and N. R. McFarland. 2000. Striatonigrostriatal pathways in primates form an ascending spiral from the shell to the dorsolateral striatum. *J Neurosci*, 20: 2369–82.

Hollerman, J. R., L. Tremblay, and W. Schultz. 2000. Involvement of basal ganglia and orbitofrontal cortex in goal directed behavior. *Progr Brian Res*, 126: 193–215.

Jankovic, J. 2008. Parkinson's disease: Clinical features and diagnosis. *J Neurol Neurosurg Psychiatry*, 79: 368–76.

Kalivas, P. W., and C. O'Brien. 2008. Drug addiction as a pathology of staged neuroplasticity. *Neuoropsychophramacology*, 33: 166–80.

Kalivas, P. W., and N. D. Volkow. 2005. The neural basis of addiction: A pathology of motivation and choice. *Am J Psychiatry*, 162: 1403–13.

Kelley, A. E., and K. C. Berridge. 2002. The neuroscience of natural rewards: Relevance to addictive drugs. *J Neurosci*, 22: 3306–11.

Li, Y., M. J. Acerbo, and T. E. Robinson. 2004. The induction of behavioral sensitization is associated with cocaine-induced structural plasticity in the core (but not shell) of the nucleus accumbens. *Eur J Neurosci*, 20: 1647–54.

Malleret, G., J. M. Alarcon, G. Martel, S. Takizawa, S. Vronskaya, D. Yin, I. Z. Chen, E. R. Kandel, and G. P. Shumyatsky. 2010. Bidirectional regulation of hippocampal long-term synaptic plasticity and its influence on opposing forms of memory. *J Neurosci*, 30: 3813–25.

Nestler, E. J., and G. K. Aghajanian. 1997. Molecular and cellular basis of addiction. *Science*, 278: 58–63.

O'Donnell, P., J. Greene, N. Pabello, B. L. Lewis, and A. A. Grace. 1999. Modulation of cell firing in the nucleus accumbens. *Ann N Y Acad Sci*, 877: 157–75.

Redish, A. D. 2004. Addiction as a computational process gone awry. *Science*, 306: 1944–47.

Redish, A. D., S. Jensen, and A. Johnson. 2008. A unified framework for addiction: Vulnerabilities in the decision process. *Behav Brain Sci*, 31: 415–87.

Robinson, T. E., and B. Kolb. 1999. Alterations in the morphology of dendrites and dendritic spines in the nucleus accumbens and prefrontal cortex following repeated treatment with amphetamine or cocaine. *Eur J Neurosci*, 11: 1598–604.

Salmon, D. P., and N. Butters. 1995. Neurobiology of skill and habit learning. *Curr Opin Neurobiol*, 5: 184–90.

Schultz, W., P. Dayan, and P. R. Montague. 1997. A neural substrate of prediction and reward. *Science*, 275: 1593–99.

Self, D. W., and E. J. Nestler. 1998. Relapse to drug-seeking: Neural and molecular mechanisms. *Drug Alcohol Depend*, 51: 49–60.

Self, D. W., R. Z. Terwilliger, E. J. Nestler, and L. Stein. 1994. Inactivation of Gi and Go proteins in nucleus accumbens reduces both cocaine and heroin reinforcement. *J Neurosci*, 14: 6239–47.

Steiner, H., and K.-Y. Tseng. 2017. *Handbook of Basal Ganglia Structure and Function*. Amsterdam: Elsevier/Academic Press.

Widnell, K. L., D. W. Self, S. B. Lane, D. S. Russel, V. A. Vaidya, M. J. D. Miserendino, C. S. Rubin, R. S. Duman, and E. J. Nestler. 1996. Regulation of CREB expression: In vivo evidence for a functional role of morphine action in the nucleus accumbens. *J Psychopharmacol Exp Ther*, 276: 306–15.

Wise, R. A. 1998. Drug-activation of brain reward pathways. *Drug Alcohol Depend*, 51: 13–22.

Wise, R. A., and M. A. Bozarth. 1987. A psychomotor stimulant theory of addiction. *Psychol Rev*, 94: 469–92.

Wolf, M. E. 2002. Addiction: Making the connection between behavioral changes and neuronal plasticity in specific pathways. *Mol Interv*, 2: 146–57.

Wolf, Y. I., G. Karev, and E. V. Koonin. 2002. Scale-free networks in biology: New insights into fundamentals of evolution? *Bioessays*, 24: 105–09.

4

Biological Risk Amplification: Disease Vulnerability

Learning Points

- **People with greater addiction vulnerability acquire the disease more easily and more rapidly than people in the general population**. They are also prone to having more severe and damaging disease courses.
- **Heightened addition vulnerability is generally *not* drug-specific although there are specific factors that can increase (or decrease) vulnerability that is specific to certain drugs.**
- **Addiction vulnerability is associated with earlier age of onset and the acquisition of multiple types of addictions (involving two or more drug classes) happening sequentially and/or concurrently.**
- **Genetic factors, including those tied with various forms of mental illness, and adverse environmental conditions (e.g., traumatic experiences) that also produce or worsen a wide spectrum of mental illness all conspire to increase addiction disease risk.**
- **The neurocircuitries of mental illness and addiction are integrated**. This convergence of pathologies represents

a fundamental design motif of the mammalian brain where the primary motivational neural network (in the NAC), which is most directly altered by addiction, is a convergence zone of projections from cortical–limbic networks (PFC, AMY, HCF) that are involved in the pathogenesis of mental illness. The integration of brain circuits involved in mental illness and addiction produce bidirectional causality and disease worsening of dual-diagnosis illness components.

- **Both *abnormal* brain states of mental illness, and *normal* brain transitions of adolescent neurodevelopment represent *common, involuntary, neurobiological* contexts that can separately or interactively amplify addiction vulnerability**. A neuroscientific understanding of how these vulnerability states increase addiction risk and produce disease acceleration translates to a better understanding of addiction disease on both the individual patient (clinical) and population (epidemiological) levels. This neuroscience of addiction psychiatry (synonymous with the neuroscience of dual diagnosis) has important implications for optimizing the prevention and treatment of addictions via the integration of mental health and addiction clinical training and treatment services.

Introduction

What Is Addiction Vulnerability?

Understanding addiction vulnerability is a key scientific bridge and translation of the basic neurobiology of addiction covered in Chapter 3 that moves us closer to the clinical level of diagnosis and treatment covered in Chapter 5. Addiction vulnerability understood at the neurocircuit level helps us explain why the disease strikes certain populations so avidly, producing a wide range of secondary medical and psychiatric consequences for them. In turn, this neuroscience, which explains why dual-diagnosis disorders are so common, has major implications for how we should diagnose and treat addictions and the mental illnesses as integrated diseases.

Chapters 2 and 3 have reviewed the behavioral and neurobiological processes that happen as an individual acquires addiction. Given that the

disease process is based within a complex neural network composed of many "parts" that are governed by vast numbers of subsidiary mechanisms and neural systems, we can expect that many factors and forces that act on or within these systems can impact the threshold or speed by which a person becomes addicted.

Many readers will agree with this observation from their own college-age experiences: Although bouts of drug experimentation and binge drinking are quite common across college campuses (e.g., about a third get into binge drinking; Krieger et al., 2018), most of these students are still able to successfully pursue their studies and transition into adult life without developing chronic severe substance use problems. Still, there is a subset that will go on to have heavy, life-threatening addictions. How can we account for the fact that many people can have similar initial exposure patterns to a substance, yet only a subset become addicted? To answer this question let's begin with defining terms:

> ***The degree of addiction vulnerability*** **can be conceptualized as individual differences in the number of "hits" (i.e., uses) of a substance that it takes for a person to develop the pathological changes in motivated behavior (and brain systems) that underpin addiction.**

Of course, reality is a bit more complicated than this. It's not just the number of "hits" of the drug it takes to kindle an addiction. It also has to do with the frequency (temporal pattern), dose, and route of use of the drug. Also, there is a "chicken or the egg" dilemma in play where, as discussed in the last chapter, addiction pathogenesis involves an acceleration of a vicious behavioral–brain cycle. More drug hits drive the addiction process, and worsening addiction increases the frequency of drug hits. But in the laboratory setting at least, many of these variables and complex interactions can be held fairly constant, so that it is possible to observe that there is a normal variance across a population of animals, in terms of how soon they start to show acquisition of addictive behaviors, and how stubbornly installed these behaviors become. That is to say, there is considerable variation of addiction vulnerability in any population of animals. For most mammals, including humans, the question is not so much about if the individual can get addicted; rather, it is about how much drug does it take, how quickly can the disease manifest, and how severe can the disease get? In terms of thinking

about severity, the observables boil down to (a) how much total damage (medical, psychiatric, financial, legal, social) the addiction is generating and (b) how hard it is to treat.

Addiction vulnerability thus varies widely across individual animals and humans and there are resilience factors that allow some individuals at the more favorable end of the vulnerability spectrum to be remarkably disease-resistant. Again, this reminds us of that friend from college who could smoke cigarettes on weekends but never go on to become a regular smoker. The wide range of addiction vulnerability in the general population reveals addiction to be a biomedical disease process similar to virtually all other major complex biomedical diseases processes of vital body organs (e.g., cancer, heart disease, type II diabetes, dementia, and so on) that are highly multifactorial and affected or accelerated by many biological and environmental risk factors. In this chapter, we will review the major genetic, environmental, neurobiological, and neurodevelopmental contexts that produce addiction vulnerability and enhance disease acceleration.

Addiction as a Heritable Disease

A vast catalogue of research has accumulated on the genetics of addiction disease risk, especially for alcohol. It is estimated that more than 1,500 genes, most of which are expressed via mRNA transcription in the brain, play a role in the variation in addiction risk. These genes are involved in many functions ranging from drug metabolism (happening in the body) to a multitude of mechanisms and systems that subserve brain function.

As is the case for understanding the genetics of other psychiatric and medical disorders, identical twin studies have been important for defining the heritability of addictions. **Heritability** is a data-supported estimation for what percentage of variation in the disease incidence can be attributed "purely" to genetics. In addiction risk and pathogenesis, there is a very rich mixture of both genetics and environmental factors that conspire together to increase disease risk. Having read Chapter 3, this should not come as a surprise for the reader because the brain (and the brain regions where addiction occurs) are profoundly and intricately sculpted, *biologically*, by both genetic determinants and environmental experiences. This interaction of many genes and environmental conditions has made it difficult or even impossible for studies focused on addiction (that look at different subpopulations) to converge on

a *narrow* range of genetic factors responsible for addiction risk. So, for example, in contrast to identical twin studies that have fairly consistently found about a 50% heritability rate for schizophrenia (roughly equivalent to the average rate of concordance of the disease among identical twins), the heritability for addiction has been characterized across studies in a much broader range, 30–80%. Some of this increased variance is also due to how addiction is defined (in terms of clinical severity) and the wide range of substances that could be involved, which each impart their own average degree of addiction risk (e.g., tobacco/nicotine is generally more addictive than cannabis/tetrahydrocannabinol (THC)). In sum, although addiction risk is highly heritable, *addiction genetics have a probabilistic effect but not a concretely predictive or deterministic effect*, because the risk is so exquisitely dependent on so many genetic and environmental factors.

Animal Modeling Alcoholism with Inbred Rats

Animal modeling, most of it involving rats and mice, has played a major role in helping us understand the complex genetic basis and neurobiology of addictions, especially in the case of alcohol. For example, the alcohol "Preferring '**P rat**'," developed and characterized at Indiana University School of Medicine since the 1970s, became one of the most widely studied and informative genetic animal models of addiction in the world. This animal model was created not by modern gene knock-out or gene turn-on technologies, but the old-fashioned way, by repeatedly inbreeding rats – generation after generation – based on whether they liked to drink high amounts of pure ethanol in water solutions (even with no flavor or sugars added). Because P rats were so well bred to prefer alcohol and did not require food reinforcers to show this phenotype, they represented excellent animal models for alcohol addiction. So, with P rats, all the following could be studied in one animal model: (a) the complex biology of genetic risk to alcohol addiction; (b) the behaviors intrinsic to and surrounding alcohol addiction; and (c) the biology resulting from toxic/chronic exposure to alcohol.

Although it was initially hoped the P rats (and other inbred rodent models) could help us define a small set of genes responsible (and specific) for alcohol addiction, they revealed a quite different and much more complex story. First, even though these rats were created exclusively

by means of selection for the trait of high alcohol consumption, the outcome phenotype of excessive drug use was not specific to alcohol! P rats also show elevated addiction risk profiles to other drugs that have very different pharmacological-intoxicating effects from alcohol, including nicotine and cocaine. Moreover, P rats, even before they are exposed to alcohol, show abnormal behaviors that can be categorized as nonspecific signs of underlying mental illness (e.g., like excessive novelty-seeking). Thus, as we will consider next, the genetic risk set of addiction is not only very complex and multifaceted, but it is also largely not drug-specific, and at the same time overlapping with the genetic risk of mental illness.

Toward A Complex Recipe for Addiction Risk

Within the genetic risk set for addiction, it is helpful to categorize these factors as falling into one of two groups: one where the genetic risk factor(s) is largely drug-specific and the other where the factor(s) (e.g., as in the P rats) increase addiction risk to multiple drugs. It turns out that both of these classes of risk factors certainly exist. But by and large, the major component of heritable addiction risk appears to be nondrug-specific. Hence, many of the genetic determinants that affect motivational neurocircuit function that are downstream from the postsynaptic DA release that different addictive drugs produce (as described in Chapter 3) could have a general addiction disease risk impact rather than a drug-specific impact.

In fact, most patients with severe addictions typically have more than one addiction (i.e., involving more than one drug) as manifested either serially or concurrently. At least two major causal dynamics (which can also happen in the same individual as compounding effects) can create this **polysubstance vulnerability**, described as follows:

(1) Cross-sensitization: In cross-sensitization, chronic exposure to an addictive drug is understood as initiating the addiction disease process in a way that not only sensitizes the brain to motivational cues specific to that drug (see sections on sensitization in Chapters 2 and 3), but also in a way that allows a second (different) addictive drug more efficiently become part of the addictive drug use pattern. This dynamic is closely related to the idea of the "gateway" drug, where the initial use of one drug, say in adolescence, is thought to increase the risk of acquiring addiction to multiple other drugs. Animal studies have broadly supported the existence of cross-sensitization

and have suggested the presence of multiple pharmacological and biological mechanisms by which it may take place. For example, taking two addictive drugs (e.g., nicotine and alcohol) at the same time might produce a stronger DA surge or postsynaptic (NAC network) impact than what the same dose of either drug alone might create. Or, if two different drugs are similar in their neuropharmacological actions (e.g., cocaine and amphetamine), then after addiction has set in with respect to one drug, the other drug might readily substitute for the other.

(2) **Brain attractor states for addiction**: In the brain attractor state for addiction, it is understood that there is an initial brain context or condition affecting the individual that confers increased addiction risk that is not drug-specific. Thus, when the individual with this condition is eventually exposed to more than one addictive drug, they are more likely to acquire addiction involving *multiple* addictive drugs. This attractor state dynamic is analogous to our understanding of how, in astrophysics, large gravitational fields of very massive objects can pull in multiple other objects into its orbit (e.g., the Earth has one moon, but the much larger Jupiter has more than 50 moons). So, when certain brain contexts or conditions that exist premorbid to addiction operate as strong addiction attractor states, they often produce polyaddictions. As we will discuss in much of the rest of this chapter, two major brain states/conditions are prime examples of this kind of vulnerability: mental illness and adolescent neurodevelopment. Again, as in the research supporting the existence of cross-sensitization, animal research has also been important for demonstrating the existence of these addiction attractor states.

Multifinality and Equifinality in the Nature and Nurture of Addiction Risk

In considering and comparing cross-sensitization and brain attractor states as mechanisms that convey nondrug-specific risk of addiction, it is important to realize that both dynamics may take place in the same individual as either separate or integrated processes. For example, an individual, "Jack," may carry a gene "C" that can get turned on in response to heavy alcohol consumption that could also (after having been turned on by alcohol) convey increased likelihood of getting addicted to cocaine. At the same time, Jack may carry a different gene "D," which enhances his

risk of having schizophrenia. But because having schizophrenia is also a kind of brain attractor state for acquiring addiction (to cocaine and alcohol), then gene "D" also counts as a risk gene for addiction. So, Jack carries at least two gene loci that work through different intermediate pathways to impart enhanced addiction risk.

Yet another individual, "Dana," may carry a gene "E" that is involved in multiple causal dynamics all at once. Gene "E" could enhance single-drug sensitization. It could also enhance cross-sensitization, and it could be a fundamental ingredient of susceptibility to schizophrenia. For both Jack and Dana, we can end up with the same phenotype: schizophrenia and polyaddictions, even though the genetic determinants for their diseases are different and work through different (albeit similar) intermediate pathways.

This "Jack and Dana" scenario, however simple, provides a glimpse at why the genetics of addiction is so complex and multideterminant, likely involving many hundreds or thousands of different genes and gene combinations. Indeed, although many genes or gene loci have been described as elemental to both addiction and/or mental illness risk, each such risk gene is not very powerful all by itself in conveying this risk. The genetic evidence on addiction thus overwhelmingly refutes the idea of simple Mendelian genetics being at work where major addiction risk is imparted through just a small number of genes (within or across individuals). In fact, the potency of any given addiction risk gene is not only small, but it is likely to be highly dependent on the presence of many other addiction risk genes *and* the particular environmental experiences that the individual has had, which may be permissive or suppressive to the activities of different risk genes. Moreover, because many addiction risk genes may not even be phenotypically pure to addiction (e.g., they could also convey risk of bipolar disorder), attempts to understand the genetics of addiction as something other than being a highly polygenetic state that is highly overlapping with the genetics of mental illness have not panned out.

Getting our heads wrapped around the complex genetics of addiction and dual-diagnosis disorders is greatly facilitated by understanding the concepts of multifinality and equifinality. In **multifinality**, an individual might carry a gene E, for example, that encodes for both addiction risk (one phenotype) and schizophrenia (a second phenotype). So, as for "Dana" in the "Jack and Dana" scenario, her one gene E imparts

increased risk of *multiple* phenotypes. But there is also the situation where you have two different genes, "C" carried by Jack and "E" carried by Dana, that both impart risk of the same phenotype of addiction. In this way, genes "C" and "E" show **equifinality**; they are different genes with different proximal functional roles that nevertheless ultimately encode elevated risk for the same (or "equal") phenotype.

A Synergy of Genotypes and Ecophenotypes in Addiction and Dual-Diagnoses Risk

In considering the large number of genes that are implicated in addiction pathogenesis (>1,000), we can reasonably hypothesize that many of them have their phenotypic effects through either multifinality or equifinality type pathways. As if this complexity was not enough, we also know that environmental experiences while growing up (or during adulthood) can also contribute *biologically* to addiction risk. The importance of environment and experience to the pathogenesis of addiction and mental illness has unfortunately been largely neglected in psychiatric research and practice over the last quarter century due in part to the tremendous resources and effort the field has devoted to defining the genetic basis of these disorders. Nevertheless, we are now entering an era of renewed interest in the neurobiological impact and behavioral consequences that various forms of psychologically traumatic experiences have on both children (encompassing childhood emotional, sexual, physical abuse and neglect) and adults (in terms of the impacts of domestic violence, crime and war trauma, racism, sexism, and extreme poverty, and so on).

In the brain, extreme environmental experiences (often termed **traumas**) can work as *biologically potent insults*. Depending on the dose (severity), degree of convergence (how many different types of traumas fall onto one person over the same time period), duration (chronicity), and developmental timing of these kinds of traumatic experiences, they can be quite neurotoxic. So, on par with what genetic determinants can do (or even what toxic drug exposures can do to the brain), traumatic experiences can produce profound changes in brain architecture and function that are long-lasting, and sometimes very difficult to reverse. With attention to the rapidly growing body of neuroscience in this area, Martin Teicher (a developmental neuroscientist and psychiatrist at Harvard) has introduced the term **ecophenotype** to represent the

phenotypic change in brain and behavior that results from a traumatic (and neurobiologically impactful) experience. This terminology is very helpful in creating a scientific and clinical framework that restores emphasis on both genes *and life experiences* as key determinants of mental illness and addiction, while also highlighting that not only are these different classes of disease-causing factors interactive, but they are *both* biologically active forces that have *both* psychological and behavioral consequences.

It is beyond the scope of this book to adequately review how traumatic experiences can change the brain on par with what genetics, drug exposures, or even mechanical mild traumatic brain injuries (mTBIs) can do. But it is important to give the reader a glimpse of some of the many brain and behavioral pathways that are involved.

A theory that enjoys broad-based empirical support from both the clinical and basic science literatures holds that traumatic experiences and experiential poverty or neglect can have a direct neurobiological impact because the brain is fundamentally a machine that is designed to adaptively respond to the environment through experiential learning (corresponding to experience-induced changes in neural wiring that result in behavioral change). Thus, major life experiences (or lack thereof) can be expected to have profound long-term effects on neural network development, particularly those networks integral to the emotional, cognitive, and motivational systems of the brain outlined in Chapter 3. Indeed, we know that traumatic experiences can generate extreme changes in both glutamate and dopamine neurotransmission (remember from Chapter 3 that both of these transmitters are key mediators of information processing and learning and memory within motivational neural networks). And, when paired with extreme fluxes of stress hormone levels (e.g., corticosteroids) or the abnormal regulation of these hormones that traumatic experiences can also generate, stress-indued glutamate neurotransmission can actually become neurotoxic, damaging axons and dendrites that interconnect neurons, or even contributing to neuronal death. Such effects are well documented in *in vitro* and animal modeling work on a microanatomical–cellular scale. These effects have also been observed (although more indirectly) in humans with trauma-related psychiatric conditions (post-traumatic stress disorder (PTSD), borderline personality disorder, depression, and so on). These patient populations show evidence of **cortical–hippocampal**

atrophy and network dysfunction as measured by neuroimaging, and abnormalities of social–emotional and cognitive functions that are tied to these systems. These changes are accompanied by alterations in neurohormonal systems (e.g., the **hypothalamic–pituitary–adrenal (HPA) axis**) involved in regulating brain plasticity needed for optimal responses to drastic changes in the environment. Two emerging and remarkably interesting frontiers in understating the neurobiology of trauma (as a foundation of addiction pathogenesis) are the fields of *neuropsychoimmunology* and *attachment neuroscience*.

In **neuropsychoimmunology**, there is growing awareness that many of the genes (or gene products) expressed in the body that are involved in immune defense overlap with genes (or gene products) in the brain that are involved in neuroplasticity. This is super interesting considering that although the immune system is geared up to protect us against microorganism attacks, most trauma-spectrum experiences involve some form of human-on-human threat or attack, or natural disaster threat or attack. Of course, it is the brain rather than the immune system that is key to responding to these kinds of large-scale, nonmicroorganism threats. However, our genetic evolution has found a way to use some of the same cellular signaling and morphological control systems (one involving the immune system, the other in the brain) to deal with both classes of threats. The key implication of all this is that too much neurohormonal responsivity happening as a result of too much human-initiated trauma and threat (or other breakdowns in human-to-human care-taking), especially as experienced during childhood, can semi-permanently "overadapt" the individual's brain to that level of insecurity and danger. This leads to increased risk of the individual acquiring certain personality disorders, PTSD, recurrent depressions, or even psychotic disorders.

Attachment neuroscience, launched by the British psychiatrist John Bowlby in the middle of the twentieth century and elaborated on by the primate work of Harry Harlow (University of Wisconsin) and others, describes the critical role that secure, engaged, and psychologically nurturing relationships (e.g., especially between children and their parents) have in contributing to long-term mental health. It turns out that chronically deficient or chaotic parental care-giving, abnormal physical contact, and/or overaggressive social interaction can have serious effects on brain development, particularly involving those neural networks that govern emotions, social behavior, and *motivation*.

In adult life, individuals who have suffered from severe parental neglect, sexual or physical abuse, and/or attachment failure as children not only show extreme risk of a wide range of mental disorders, *including addictions*, but they are also at risk of propagating the damage transgenerationally, because their own damage can prevent them from forming healthy secure attachments to their own children. Although a thorough review of the biology of how this happens is beyond the scope of this book (and much remains to be discovered), **oxytocin** has emerged as a key neurohormonal factor that is involved in healthy attachment formation between both children and their parents and between adults in close relationships. The endogenous opioid system is also involved in the development and regulation of brain systems that mediate healthy attachment.

A bottom line for both the neuropsychoimmunological and attachment neuroscience underpinnings of traumatic experiences is that *all of these pathophysiological pathways lead to both mental illness and heightened addiction risk*. In other words, extreme environmental experiences produce **ecophenotypes** that work biologically with **genotypes** to produce disease outcomes of comorbid mental illness and addiction risk via both **multifinality** and **equifinality**. Understanding this complexity is made easier when we give up on trying to assume that simple Mendelian genetics is key for understanding mental illness or addiction, and we let go of mythologies that promote strict dichotomizations and splitting between nature versus nurture, mind versus brain, psychology versus neurobiology, and mental illness versus addiction. In fact, both the genetic and environmental ingredients that produce different forms of mental illness and addictions are so overlapping and interactive, in terms of generating abnormalities of brain development and integrated neurocircuit function (that govern motivation, cognition, and emotional control), that it should be no surprise that mental illness and addictions often occur together – and biologically drive one another – to a very high degree, so that dual diagnosis emerges as a mainstream public health problem.

Thus, analogous to the structure of a tree, the wide range of genetic and environmental risk factors that generate addictions and dual-diagnosis disorders can be thought of as a list of ingredients (roots of the tree) that contribute to the pathological neuroanatomy of dual diagnosis (trunk of the tree), by which mental illness *causes* increased addiction risk and

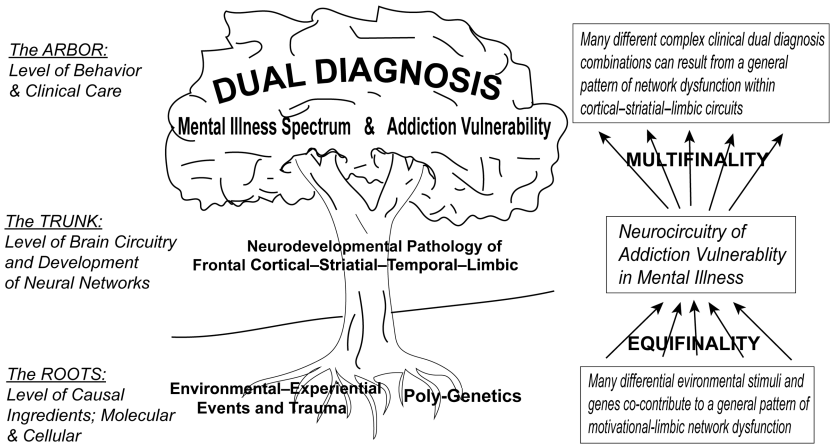

Figure 4.1 Developmental pathogenesis of mental illness and addiction: the integrated tree of dual diagnosis. The causal ingredients, developmental neurocircuitry, and clinical phenomenology of addiction and mental illness are integrated processes that resemble the structure of a tree. This integration of pathological processes reflects the fundamental network architecture of the mammalian brain where decision-making/motivational circuits (PFC/NAC) are directly and densely connected with circuits that mediate emotion (AMY) and short- and long-term memory (vHCF).

severity, generating a wide spectra of dual-diagnosis clinical presentations (arbor of the tree; Figure 4.1).

In this formulation, it is more accurate to view the genetic and environmental "ingredients" as causal elements that do not by themselves represent the neural mechanisms of dual-diagnosis disease comorbidity. Rather, these ingredients are like actors in the plot, and it is actually the plot (of many actors) that represents the disease mechanism. This is because the disease mechanism of dual-diagnosis comorbidity is so highly polygenetic and contributed to by so many complex environmental conditions – and is happening on so many scales of brain function (spanning molecular, neurochemical, cellular, neural network, regional, and global anatomical scales). For our best, most comprehensive view on the neuroscience of addiction psychiatry, the focus needs to be more on the plot of the story (rather than only one or a few of the many actors that play in it). Thus, we need a systems perspective that illuminates what is happening on the scale of

motivational neural networks that incorporates what we reviewed in Chapter 3 to understand how mental illness accelerates addiction risk. Moving forward with this approach, we will consider the pathophysiology of addiction with an overlay of what is happening in the brain when the addiction–attractor states of mental illness and adolescent neurodevelopment are in play.

Neuroscience of Dual Diagnosis: Mental Illness Amplification of Addiction Vulnerability

Bidirectional Causality in Mental Illness–Addiction Pathogenesis

Although the association between mental illness and addiction is very clear to psychiatric clinicians and is overwhelmingly supported by the epidemiological evidence, the rigorous discovery, characterization, and testing of the *causal mechanisms* that drive this association has be difficult to accomplish and limited when pursued exclusively on clinical and epidemiological levels of investigation. Certainly, a wealth of clinical evidence has accumulated over many decades, making it clear that heavy, uncontrolled use of virtually all addictive drugs spanning cocaine, amphetamines, opioids, alcohol, cannabinoids, nicotine, and so on can at least transiently produce or worsen psychiatric symptoms (e.g., during acute intoxication and/or withdrawal). Many of these drugs, especially alcohol, are also well known to be able to produce longer-lasting changes in brain anatomy and physiology leading to more permanent neuropsychiatric conditions (e.g., consider alcohol neurotoxicity in **fetal alcohol syndrome**, or **Wernicke–Korsakoff's syndrome** with its alcohol-induced dementia of adulthood). This form of causality – where drug use causes mental illness (as either transient cognitive–emotional symptoms or as a long-term syndrome) is so routinely observed and well-established clinically that we really don't need direct experimentation to prove that it happens. In fact, we are so firmly sure that it can and does happen that it wouldn't even be ethical to try to prove that this causality exists in controlled, prospective human experiments. For example, there is no legitimate **institutional review**

board (IRBs are committees charged with providing ethical oversight for studies involving human subjects) that would approve of a human-subjects study that aims to demonstrate that given enough alcohol, a researcher can make an otherwise healthy adult become demented, or, given enough methamphetamine, the investigator can cause a substantial number of people to develop a long-lasting psychosis, or bipolar-like illness, or addiction, and so on.

So, it is well accepted that substance use, especially heavy, chronic forms, at least temporarily induce mental illness-like syndromes. But what about the flip side of the causal relationship between mental illness and addiction? *How do we show that the causal relationship is bidirectional – also happening in the opposite direction where mental illness is a root cause, illness exacerbator, or biological vulnerability state of addiction?* As we discuss in the "myth-busters" section of Chapter 2, a longstanding and quite dominant hypothesis that entertains this direction of causality is the "self-medication hypothesis" – the idea that people with mental illness use drugs so much because drugs somehow alleviate their symptoms. An interesting implication of this hypothesis has been that because it merely assumes that drug exposure must have a benefit for mental illness, then it is more ethically testable in humans (regardless of whether it is actually true). Thus, it would be much easier to get a study approved by an IRB to show, for example, that introducing a nicotine patch for a patient with dementia might slow progression of the dementia than it would be to do the same study if the expected or to be proven outcome pertains to the acquisition of nicotine addiction, or nicotine-induced mood disorders, or strokes in demented people.

Regardless of the relative amenability of the self-medication hypothesis to human research (which is one of the reasons this flawed theory has held on for so long in psychiatric research), one of the major weaknesses of the hypothesis comes precisely from the evidence we have considered above: A major part of the causality that contributes to the association between mental illness and substance use is flowing in the opposite direction from what the self-medication hypothesis asserts (i.e., where chronic, heavy drug use worsens or generates mental illness). Thus, as pointed out in Chapter 2's Myth-Busters, it is illogical to accept the idea that we can explain the tight association between mental illness and substance disorders as happening because heavy drug use reduces

mental illness, when by and large the data are clear that heavy drug use generates psychiatric symptoms and worsens mental illness.

It turns out there is a straightforward way we can avoid this logical–empirical failure of the self-medication hypothesis and still consider a plausible causal direction starting from mental illness leading to heavy substance use, even though heavy substance use *worsens* mental illness. *All that's needed is to consider mental illness as being a disease accelerator of addictive risk and severity.* This perspective understands enhanced addiction risk as a fundamental biological feature inherent to many forms of mental illness. In this "**primary addiction hypothesis**" (first described by Chambers et al. in the case of schizophrenia in 2001), the causal relationship between mental illness and addiction can be considered bidirectional, but without being conflicted or illogical (as happens with the self-medication hypothesis). The logical coherence of the primary addiction hypothesis is anchored on the fact that addiction pathogenesis, by definition (see Chapter 1) encompasses *compulsive drug use despite negative consequences.* So, with mental illness and substance use, we have a perfect storm of bidirectional causality on our hands, described even in the very definition of addiction itself: mental illness (or symptoms of it) is a negative consequence of compulsive drug use, even as mental illness can pathologically accelerate the process whereby drug use becomes compulsive (Figure 4.2). In this kind of bidirectional disease synergy, we not only have a clear explanation for why mental illness and addictions so usually occur together, but we also have an explanation for why increasing degrees of mental illness severity correspond to increasing degrees of addiction risk and severity. As we will describe in Chapter 5, this science also has significant translational implications for treatment delivery.

A scientific challenge with this primary addiction hypothesis of mental illness, despite how well it sidesteps virtually all the logical and empirical failures of the self-medication hypothesis, is that you cannot ethically conduct a prospective, controlled study in humans necessary to demonstrate that it is true (i.e., no well-controlled, human study could be done ethically to prove it). For example, no IRB should ever approve a study that would randomize groups of healthy versus mentally ill 18-year-old boys to snorting a line of cocaine once a day for 10 days to see which group acquires greater rates or severities of cocaine addiction.

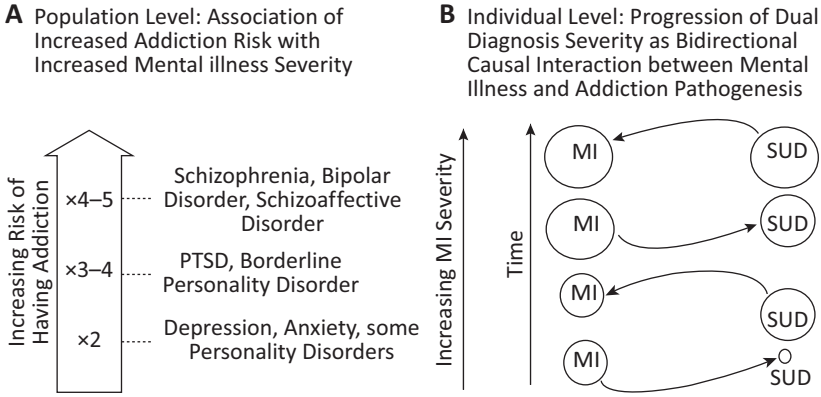

Figure 4.2 Interactive causality of risk and pathogenesis of mental illness and addiction on the population and individual levels. **A**. On the population level, increasing severity of underlying mental illness (MI) is generally associated with greater likelihood of acquiring addiction and greater addiction severity. **B**. On the individual case level, mental illness elevates substance use disorder (SUD)/addiction risk (directional arrow from MI to SUD). Then as the SUD is acquired and becomes heavy, it can rebound to increase MI severity. The underlying MI continues to accelerate SUD severity and risk of acquiring multiple forms of addition; active heavy multidrug use in polyaddiction further exacerbates underlying MI symptomatology and risk of medical morbidity and mortality.

So, how do we get around this ethics problem to do the science we need to find empirical support for the primary addiction hypothesis? This is where animal modeling has come in very handy. We have the rats to thank for showing us much about how mental illness accelerates addiction acquisition and severity.

Animal Modeling as a Key Approach to Addiction Psychiatry Neuroscience

It turns out that addiction, among all psychiatric diseases, is arguably the most amenable to animal modeling research, because the symptoms of the disorder are objectively measurable through behavior (drug use) and do not rely heavily on subjective–verbal symptom reports, which rats cannot provide. Also, the inciting elements of addiction – the drugs themselves – produce concrete pharmacological and biological actions in the brain providing key mechanistic clues about addiction

pathogenesis. Such concrete inciting elements are just not as available to us for unlocking the mysteries of pure mental illness.

So, we have excellent rat models of addiction. But do we have rat models of mental illness? Absolutely we do, and in fact we have over a hundred different ones that vary widely in terms of which mental illness they model (e.g., schizophrenia or PTSD), what etiological methods are used to create them (e.g., a brain lesion, a gene knockout, heavy exposure to a neurotoxic drug, exposure to repeated stress, or combinations thereof), and the quality and scope of symptoms. Different models can be used to produce narrow (**endophenotypic models**) versus broader sets of symptoms (**comprehensive** or **syndrome models**) consistent with a given human disorder. For asking how mental illness may accelerate addictive disease in the preclinical laboratory, the investigator needs to judiciously choose an appropriate animal model of mental illness and then see how avidly those animals acquire addiction compared to healthy animals.

Part of the process in selecting good animal models of mental illness for testing addiction acceleration, comes from considering what we already know about how the neuroanatomy of the key brain regions of mental illness and addiction intersect. Building on Figures 3.1 and 3.2 where we diagramed the key neurocircuitry of motivation, we now need to consider the key brain regions that are involved in the pathophysiology of the major mental illnesses. It turns out that the PFC, AMY, and HCF have all been variously implicated across a vast wealth of studies that have characterized what is pathologically altered in the brains of people with schizophrenia, bipolar disorder, depression, PTSD, personality disorders, and many other psychiatric illnesses. An important neuroanatomical fact to also know is that all of these key brain regions, the PFC, AMY, and HCF – aside from being pan-implicated in mental illness – are also directly wired into each other *and the NAC /ventral striatum neural network*.

Thus, not only are:

> **All the brain regions chiefly implicated in major mental illness directly connected with primary motivational circuits altered by addiction**

but also (see Chapter 3):

> **These distributed systems (PFC, AMY, HCF) send physical connections (axons) and neural information streams that *converge***

into the *NAC/ventral striatum* as a means to *inform* and (based on experience) *restructure* and *revise* motivated behavior.

The significance of these themes for understanding the connection between mental illness and addiction becomes clear when considering that addiction is essentially a *pathological* restructuring of motivated behavior (as detailed in Chapter 3). So, the pathology of addiction, as it occurs in core motivational circuits (i.e., the NAC), can be expected to be augmented, if the NAC is already pathologically interconnected (in the context of mental illness) to other limbic regions that should under normal circumstances inform healthy motivation. In other words, the neuroanatomies where addiction and mental illness occur are totally wired into each other; these diseases are anatomically and biologically predestined to be interlinked!

Although this anatomy indicates how the mammalian brain is built in a way such that the pathogenesis of mental illness and addiction are often inextricably interlinked, animal models are still needed to demonstrate this linkage behaviorally, and to find out more about *how* they are linked causally and mechanistically. For this kind of investigation, we first need to apply animal models of mental illness in which one or more of these key brain regions (PFC, AMY, HCF) are disordered in ways that substantially simulate what is known to be characteristic of these brain systems in human mental illness. Second, it is important that the animal model of mental illness has several other behavioral and biological attributes that map credibly onto known illness attributes of the human condition (e.g., a comprehensive model). Third, we want good "construct validity" for the mental illness model as a "dual-diagnosis" condition, which is possible if the class or type of human mental illness we are trying model in the animals is also known in humans to encompass high levels of addiction comorbidity.

In a 25-year span of animal studies starting at Duke in 1995 then moving to Yale and Indiana University Medical Schools (and onto other labs around the world), the neonatal ventral hippocampal lesion (NVHL) rat model of schizophrenia has been a highly productive research platform with respect to all three of these criteria for animal modeling addiction vulnerability in mental illness. Originally developed and characterized by Barbara Lipska, Danial Weinberger and colleagues at the NIMH in Washington, DC (see Lipska et al., 1993), the NVHL model is

produced by causing neurotoxic damage to the ventral hippocampal formation (vHCF) in very young (e.g., 7-day-old) rats. In rats, this neurodevelopmental age is roughly equivalent to the second to early third trimester of human prenatal neurodevelopment – a time window when various lines of evidence suggest the human brain is susceptible to developmental insults that can seed schizophrenia later in life. Initially, in the rats, this damage is very focal. In fact, the acceptable target zone for the damage in the baby rat's brain (vHCF) is on the order of 1 mm in diameter (which makes accurate reproduction of the lesion a technical challenge!). However, the secondary effects of the damage become much more widespread and distributed throughout the brain as the rat grows up. This is because of where the lesion is located, and how the target zone is normally wired into other limbic areas over the course of postnatal development. The vHCF is not only bidirectionally cross-wired with the amygdala (Figures 3.1 and 3.2) but it also projects directly into PFC and NAC microcircuits. This means that healthy versus abnormal ventral hippocampal development has significant implications for the normal development and function of these other limbic regions. If the vHCF microcircuit is disrupted, then there is a progressive domino-like effect, taking place over the course of postnatal to adult development on the architecture and function of the AMY, PFC, and NAC networks as well. In this way, Lipska and Weinberger's developmental model of schizophrenia ingeniously incorporates both the focal neurodevelopmental problems (involving abnormal hippocampal development and anatomy) and distributed network features (encompassing atrophy of the PFC and AMY) of human schizophrenia. Lipska and colleagues went on to show that not only was the gross neuroanatomy of the NVHL model accurate to human schizophrenia, most of the major neurodevelopmental, behavioral, pharmacological, and neurophysiological features of the model were as well. Finally, meeting the third criterion for a good animal model of a human "dual-diagnosis" condition, the NVHL model is an excellent platform for understanding schizophrenia, which among all mental illnesses is one of the most highly comorbid with substance use disorders (i.e., it has some of the highest rates of co-occurring addictive diseases among mental illnesses to the extent that nearly 90% of schizophrenia patients are "dual-diagnosis" patients).

In 2002, the first work characterizing accentuated addiction vulnerability (to cocaine) in the NVHL model was published in *Neuropsychopharmacology*.

While helping to advance a new genre of animal modeling focused on dual-diagnosis disorders, this study demonstrated for the first time that the same neurodevelopmental abnormality could lead to *both* major mental illness and accelerated addiction disease. This form of **multifinality** (i.e., where the same underlying neurobiological abnormality leads to two behavioral disorder phenotypes) hinted at the core connectedness that exists between many types of mental illness and addiction. Subsequent studies using the NVHL model also demonstrated that the addiction vulnerability was not specific to cocaine, but was general to other addictive drugs (e.g., including nicotine, alcohol, and methamphetamine). Also, this addiction vulnerability was shown to be *involuntary* in that it did not require the animals' decision or action to self-administer the drug: When researchers administered the drugs involuntarily and chronically to NVHL versus healthy rats, the NVHL animals showed increases in addiction-related phenotypes that are neither drug- nor intoxication-specific. Further, this elevated addiction risk was not shown to be accompanied by any clear "benefit" or medicinal value that the drugs could specifically impart to the mentally ill animals (e.g., as the self-medication hypothesis would predict). Indeed, and particularly in the case of cocaine, the addiction vulnerability of the mental illness model was also associated with increased capacity of the drug intake *to exacerbate* the underlying mental illness. Hence a bidirectional exacerbation of mental illness and addiction was demonstrated.

In parallel to the NVHL model, other forms of mental illness models in rats that also alter frontal cortical–striatal/temporal limbic (PFC/NAC/AMY/HCF) circuit function in different ways (e.g., via olfactory bulbectomy, severe environmental stress, impoverished rearing, polygenetic addiction models) have also been shown to produce complex, co-occurring mental illness/addiction phenotypes, reflecting the equifinality-like nature of dual-diagnosis conditions, in which different biological/environmental/neurodevelopmental factors can lead to dual-diagnosis phenotypes. Together, these preclinical findings map very well to what we see in the human epidemiology spanning the dual-diagnosis spectrum in which high rates of mental illness and addiction comorbidities occur "across the board" in pervasive patterns that are neither mental illness nor drug type specific.

The Neurocircuit Basis of Addiction Psychiatry: How Mental Illness Accelerates Addiction

As the NVHL model has proven to be useful for understanding both mental illness pathogenesis and heightened addiction risk as being tightly interconnected disorders – or even one and the same – it has also served as a platform for observing on a more brain-mechanistic level how mental illness *accelerates* addiction pathogenesis. This acceleration then leads to a more severe addiction disease phenotype. To better understand the mechanisms that underpin this **acceleration of addiction**, we want to focus on how circuits effected by mental illness impact those involved in addiction.

An additional key phenotypic feature (behavioral abnormality) of the NVHL model is that in adulthood these rats are generally impulsive, showing an array of impulse control-related cognitive impairments that involve the PFC. Neurobiologically, and in parallel to these behavioral issues, these rats show quite a long list of molecular, neurochemical, cellular, and neural network abnormalities of the PFC. Remembering that the NVHL model is generated (or "unleashed!") by neonatal excitotoxic damage delivered to a zone within the hippocampus (the ventral part) in 7-day-old rat pups, it becomes clear that these PFC abnormalities are secondary consequences, downstream in anatomical space and developmental time from the original vHCF hit. In fact, this is exactly what electrophysiological studies of the PFC of NVHL rats show: as NVHL rats develop from their rat "childhoods" through adolescence and into young adulthood, the principal pyramidal neurons (see Figure 3.6) and local inhibitory neurons in their PFCs show increasingly abnormal regulation and activity of their firing patterns. Anatomically, PFC neural networks in NVHL rats also show loss of interconnectivity, increased cell packing, and overall atrophy of cortical layers. These biological abnormalities quite accurately resemble what we see in the brains of humans with schizophrenia, and they account in part for why we see similar PFC-based *behavioral and cognitive* abnormalities in both the NVHL model and schizophrenia.

Importantly, impulsivity and PFC-based neural network abnormalities are not specific to either the NVHL model or human schizophrenia. Rather, these themes are pervasive across many forms of mental illness

(and basically all those that involve increased addiction risk) and in patients with addiction disorders spanning all the major addictive drug groups. In other words, PFC dysfunction (and its behavioral manifestation of impulsivity), represents an **endophenotypic** "keystone" of dual-diagnosis pathogenesis, where mental illness and addictions are biologically and phenomenologically interlinked. This is not to say that every different type of mental illness that accelerates addiction risk (e.g., schizophrenia, bipolar, depression, PTSD, borderline personality, and so on) has the exact same biological abnormality pattern in the PFC, or the same form of behavioral impulsivity. And certainly, these differential psychiatric diagnoses are underpinned by differential forms and patterns of neural network problems in other subcircuits as well (e.g., spanning AMY, HCF and many other regions) that also impart illness-specific features to these conditions. Nevertheless, it appears to be the case that these differential disorders involve PFC-based functional problems that create impulsivity-spectrum conditions (variously labeled as "executive-decision making problems," "lack of insight," "lack of judgment," "disinhibition," and so on) that are similar enough to produce comparable downstream effects on NAC (ventral striatal) motivational networks and addiction pathogenesis. Ultimately, most of the "dual-diagnosis spectrum mental illnesses" – and especially the most severe ones – do involve some form of distributed frontal–cortical–temporal limbic network dysfunction in which two or even all three of the key regions implicated in mental illness (PFC, HCF, and AMY) are all pan-involved in the individual's illness in some way or to some degree. Then, as all three of these key brain areas (implicated in mental illness) also project directly into the NAC (implicated in addiction pathogenesis), it should follow that having mental illness in the brain can be expected to have an impact in altering the natural disease course of addiction within the brain. Accordingly, we can begin to understand the connection between mental illness and addiction as representing an unfortunately all too common vulnerability of an otherwise highly efficient and powerful design motif of the mammalian brain. In this architecture, the primary motivational neural network is directly and intricately regulated by distributed limbic regions that control cognition, expectations, memories, and feelings. The NVHL model has thus proven itself to be a particularly useful neuroscientific and behavioral model of dual-diagnosis pathogenesis, even beyond schizophrenia, because it encompasses multiple mental illness symptoms including impulsivity (which is not specific to any one mental illness) and

heightened addiction vulnerability (which is not drug-specific). It also entails developmental neural network abnormalities that span all three of the key cortical–limbic centers (PFC, HCF, and AMY regions) that are (a) cross-implicated in mental illness and (b) project into the NAC where motivation is most directly damaged in the addiction disease process.

Three Animal Modeling Studies Illuminating Mechanisms of Mental Illness Addiction Vulnerability

A series of three studies looking at the effects of a chronic, *behaviorally sensitizing* regimen of cocaine injections in NVHL rats has advanced our understanding of how abnormal frontal cortical–striatal circuitry of mental illness can accelerate addiction pathogenesis. To introduce this research, we need to return briefly to the topic of *sensitization*. As discussed in Chapters 2 and 3, sensitization is a core pathological growth process in addiction that has both biological and behavioral dimensions. In **motivational sensitization**, as the drug is repeatedly used by the individual, they subjectively experience a growth in urges and craving associated with a growth in motivation to use the drug even more. This growth process drives increases in the frequency and amounts of drug use over time, the loss of normal decision-making and control over drug use, and the displacement, subservience, and/or sacrifice of healthy motivations and behaviors in favor of drug acquisition and use. A gold standard way of generating and modeling this disease process (motivational sensitization to an addictive drug) in animal models, of course, is to allow them to acquire **self-administration** of the drug, where they learn how to acquire and use the drug on their own (typically via oral or intravenous routes). Then the researcher can observe how the drug use pattern grows over time, how animals may work harder to get the drug, and how the drug use becomes more compulsive and automatic (despite consequences). As mentioned above, precisely this kind of addiction modeling work has been done in NVHL–schizophrenia model rats, which show accelerated patterns of cocaine, nicotine, and alcohol use in self-administration studies, resulting in greater, more efficient installment of compulsive drug use behaviors compared to rats with healthy brains.

A parallel experimental approach to modeling addiction pathogenesis is the **behavioral sensitization paradigm.** Compared to self-administration experiments, which more directly reveal motivational sensitization, behavioral sensitization is technically a much easier and quicker paradigm to perform in the lab, while being safer for animals and easier to measure outcomes for. In behavioral sensitization, the researcher delivers doses of the addictive drug to the animals over time, instead of the animals self-administering the drug to themselves. Also, the outcome being looked at in behavioral sensitization (i.e., the behavior that is growing) is more concretely simple to measure and observe. Rather than it being a quantification of the accumulating pattern of drug use behavior (e.g., lever pressing for drug deliveries) or amount of drug being consumed as in self-administration, behavioral sensitization studies measure how the animal's motor programming evolves over time (days to weeks) as the animal *involuntarily* receives repeated drug doses. Typically, this measurement focuses on how much the animal moves around, couched as locomotor distance traveled, for a given period of time (typically 30–90 minutes) in an arena where the animal has just received the drug. What is quite remarkable about behavioral sensitization is that, in parallel to motivational sensitization, animals are observed to show abnormal increases in locomotor activity responses to the drug in the arena, day after day, with as few as one hit of the addictive drug per day. Notably, this growth pattern does not reflect increases in intoxication, *because it occurs even as the animals are being given the same exact dose of the drug day after day, during which time they are becoming more tolerant to the intoxicating effects of the drug* (i.e., intoxication levels are weakening over time after each dose). The resulting behavioral sensitization growth curves also closely resemble learning curves (even as the animals are not voluntarily trying to learn anything). Also, in parallel to what we understand happens in addiction in terms of motivational sensitization, behaviorally sensitizing drug regimens have a long-term impact on brain and behavior. An animal that has been behaviorally sensitized to cocaine will continue to show an abnormally elevated locomotor response to a new dose of cocaine for weeks and even months after their last cocaine dose (that was part of a prior sensitizing series). As we see in addiction, essentially all addictive drugs (including cocaine, amphetamines, nicotine, alcohol, opioids, and so on) can produce behavioral sensitization, regardless of their differential intoxication profiles, and

even though some of them are CNS stimulants whereas others are CNS depressants. So, the behavioral sensitization effect is a simple and direct way to examine how repeated doses of addictive drugs *involuntarily* change the brain and behavior in a lasting way, in large part via invoking neuroplastic changes in ventral (NAC) and dorsal (CA-PU) striatal circuits that control motivated behavior and motivational-behavioral learning. Essentially, in behavioral sensitization, repeated delivery of the addictive drug causes abnormal increases in (and compulsive-like selection of nonspecific exploratory locomotion), which (with saline injections) should normally habituate or go away with repeated exposures to the same arena where the behavior is being measured. Notably, the abnormal elevations in drug self-administration that occur in NVHL rats (measuring motivational sensitization involving cocaine, alcohol, and nicotine) has also been confirmed with respect to behavioral sensitization. Compared to rats with healthy brains, NVHL rats also show leftward and upward shifted behavioral sensitization curves to cocaine, alcohol, and nicotine, and more robust, chronic retention of these imprinted drug-response effects over time.

In three different studies looking at how mental illness and addiction pathogenesis may synergize neurobiologically, the behavioral sensitization paradigm has been used as it allows precise control and balancing of how much addictive drug each experimental group may get. Also, the involuntary nature of the disease process is directly and unambiguously observed, as it is the researcher (not the animals themselves) who is delivering the drugs. So, with behavioral sensitization, it is possible to observe how the mental illness biology can accentuate the drug sensitization process *both behaviorally and biologically, and as a completely involuntary process*, even when the cumulative dosages delivered to the mentally ill versus healthy brain treatment groups are exactly the same.

The experimental set up of these three studies followed a similar design: NVHL and healthy rat groups were randomized into saline versus chronic cocaine exposure (behaviorally sensitized) groups. Thus, these studies all followed a 2 × 2 cell design motif in which the presence of mental illness (or not) was crossed with an addiction drug history (or not), creating four different study subgroups modeling a clinical spectrum of dual-diagnosis comorbidity as follows: (1) healthy brain/nonaddicted; (2)

mentally ill/nonaddicted; (3) healthy brain/addicted; (4) mentally ill/addicted. Notably, multiple behavioral studies have established that in this order of progression ($1 < 2 \simeq 3 < 4$), these groups show increasing levels of locomotor activation in response to a challenge injection of cocaine occurring weeks after the initial injection series (of saline versus cocaine, alcohol or nicotine). That is, in the NVHL rat model preparation, there is a mental illness–based amplification of long-term sensitization to cocaine (and other addictive drugs) that is clearly observable and reliably reproduceable.

In Study #1, **a brain microdialysis study** (Chambers et al., *Psychopharmacology*, 2010), it was shown, as a replication of prior findings, that cocaine challenge injections elicit greater locomotor responses if animals had previously experienced prior cocaine sensitization, or if they were NVHL rats. As usual, NVHL rats with prior cocaine experience showed the greatest response among all groups (i.e., NVHL and cocaine history in the same rats produced the most extreme sensitized phenotypes). However, when looking directly at what was happening with the levels of cocaine-induced DA efflux into the NAC in these animals (brain microdialysis allows for real-time measurement of neurotransmitter levels in specific brain areas in awake, behaving animals) when they were receiving cocaine challenge injections, an interesting pattern of results emerged. There was actually *no* corresponding growth in the levels of DA efflux into the NAC caused by the animals having a prior cocaine history, or by having NVHL lesions, or both. In other words, although the cocaine delivery did cause a massive burst in DA into the NAC (as would be expected by the addictive drug delivery), the acquisition of greater extremes of the behavioral sensitization phenotype (which prior cocaine history and the NHVL model both produced, with the combination producing the greatest behavioral extreme) did not actually correspond to any increase in the size of the DA efflux produced by the cocaine injections. This finding highly suggested that the addiction process and its acceleration/amplification by mental illness *were not* determined by pathological changes in the amount of DA efflux that a cocaine injection produces. This finding indicated that these disease states were more directly reflective of brain changes that had occurred *postsynaptic to the DA release*, involving striatal networks that DA neurotransmission regulates and mediates plasticity for.

In Study #2, **a neural activation mapping study** (Chambers et al., *Biological Psychiatry*, 2010), a molecular marker of nonspecific neuronal

activation (**c-Fos**) was used to examine how striatal (ventral versus dorsal) regions and prefrontal cortical networks (medial prefrontal cortices versus posterior frontal cortices) were differentially activated by cocaine challenge injections based on rats having had a prior cocaine sensitizing history, being NVHL animals, or both (addiction and mental illness models combined). Notably, these anatomical selections dichotomized regions fairly accurately into circuits primarily involved in motivational processing (medial PFC/ventral striatum (NAC)) versus motor processing (posterior frontal cortex/dorsal striatum(CA-PU)) (see Figure 3.3). The results confirmed that the addiction-related phenotype (drug sensitization) was indeed encoded by brain changes occurring in cortical–striatal neural networks that were *postsynaptic* to the DA release (consistent with Study #1), and that NVHL-induced abnormalities in these same regions were exacerbating the addiction-related effects. More specifically, *a prior sensitizing cocaine history* increased the level of dorsal striatal (CA-PU) neural network activation (and its ratio of activation compared to the ventral striatum (NAC) that occurred with a challenge cocaine injection). Also, as would be expected (given that the dorsal striatum encodes and executes well-learned motor programs), across all the animals and treatment groups, dorsal striatal (CA-PU) activation was tightly correlated with degree of cocaine-induced locomotion. In summary, these findings demonstrated that the dorsal striatal (CA-PU) network was operating as a motor output system, and that prior cocaine-induced neuroplasticity (which produced the behavioral sensitization effect) was related to neural connection changes in the striatum that allowed ventral striatal (NAC) activation (which encoded the motivation to perform exploratory locomotion) to more efficiently and powerfully instigate and maintain locomotor activity encoded in the dorsal striatum (CA-PU). Based on the resulting animal data from all the rats in the study, it was possible to mathematically model this cocaine-induced behavioral sensitization data as:

Equation 1: Chronic Cocaine History Effect

$$(\textit{dorsal striatal } (CA-PU) \textit{ activation}) \simeq d(\textit{ventral striatal } (NAC) \textit{ activation})$$

where *dorsal striatal (CA-PU) activation* was proportional to (symbolized by "$\simeq$") a coefficient d (that was larger if the animal had a cocaine injection history: e.g., 0.74 with cocaine history versus 0.56 with saline

history) multiplied by the level of *ventral striatal (NAC) activation*. Again, as mentioned above, the dorsal striatal (CA-PU) activation was also tightly proportional (across all animals) to actual behavior (levels of locomotor activity post cocaine challenge injection in the arena). In essence, this expression shows how, in simple mathematical terms, the cocaine history had a cumulative, sustained neuroplastic effect that increased the ability (or efficiency) of the motivational system to call up and maintain the locomotor codes represented in the dorsal striatum, which generated the extremity of the behavioral sensitization phenotype (the addiction model).

In contrast to the cocaine effects, the NVHL model caused the animals to show a pathological *decrement* in medial prefrontal cortical (PFC) network activation (i.e., they were "**hypofrontal**"), which is a well-known characteristic of human schizophrenia and other forms of severe mental illness that involve PFC dysfunction and related cognitive deficits. Interestingly, this hypofrontality was also associated with a proportional *increase* in *dorsal striatal (CA-PU) activation*, in parallel to what cocaine history could do (in healthy non-NVHL rats), but even without a prior cocaine history being present in the case of the NVHL animal. So, it was also possible to make a simple mathematical statement that reflects this mental illness-based effect:

Equation 2: Mental Illness Effect

$$(\boldsymbol{dorsal\ striatal}(\boldsymbol{CA-PU})\ \boldsymbol{activation}) \simeq (\boldsymbol{secondary\ motor\ cortex}) / (\boldsymbol{medial\ PFC})$$

In this expression, the *secondary motor cortex* activation serves as a control region for ambient neuronal activation levels that are not strongly influenced by either cocaine or NVHL history. So, the ratio of *secondary motor cortex* to *medial PFC* activation gets larger as *medial PFC* activation gets lower. Thus, with greater hypofrontality (e.g., corresponding with more severe mental illness), the quotient (*secondary motor cortex*)/(*medial PFC*) gets larger.

Finally, it was possible to model how Equation 1 (reflecting how the chronic cocaine history changed activation in the network) and Equation 2 (reflecting how the mental illness model changed activation in the network) could interact to generate different levels of *dorsal striatal activation* (and degree of behavioral sensitization) across the entire set of animals in the experiment. Remarkably, it was found that a very simple

integration of these two equations in the form of a simple multiplication could tightly model all the animals in the experiment:

Equation 3: Integrated Effects of Addiction and Mental Illness= (Equation 1) × (Equation 2)

$$(dorsal\ striatial(CA-PU)activation) = d(ventral\ striatal\ (NAC)\ activation)\ (secondary\ motor\ cortex)/(medial\ PFC).$$

In words, this mathematical expression states that the overall degree of dorsal striatal (CA-PU) neural network activation across the animals (and their corresponding levels of behavioral sensitization, representing the severity of the addiction disease process) was shown to be a simple multiplicative product of (1) the drug-induced neuroplastic effects due to the prior cocaine history within the striatum and (2) the mental illness–based cortical–striatal network alterations present in the NVHL model. Thus, mental illness, in a totally involuntary way, but in a way that is mathematically measurable (and neurobiologically observable), *amplifies* the addiction disease process within cortical–striatal circuits.

In Study #3, **a gene-expression mapping study** (Chambers et al., *Genes, Brain and Behavior*, 2013), NVHL versus healthy control animals had their frontal cortical/ventral and dorsal striatal circuits biologically examined again 2 weeks after a cocaine sensitization (versus a saline injection series), but this time looking at genome-wide **mRNA expression patterns** using **microarrays** that contained >24,000 gene products (probesets). This time, in contrast to Study #2 where acute cocaine-challenge–induced neural activation was the sole biomarker of interest, there was no acute cocaine-challenge injection delivered at the time of the brain examination (sacrifice of rats). So, this design could provide a view on the enduring molecular/cellular changes induced by the prior addictive drug (cocaine) history and the mental illness (NVHL) model, unimpeded or masked by any recent cocaine exposure.

Here, and in patterns that replicated themes observed in Study #2, NVHLs predominantly downregulated gene expression in the *medial PFC*, while causing abnormal upregulation in the *dorsal striatum (CA-PU)*. These data revealed yet another manifestation of the hypofrontality produced by the NVHL model, this time showing up as a relative impoverishment in

neuronal gene expression (consistent with the loss of cocaine-induced neuronal activation in the medial PFC in NVHLs observed in Study #2). Also, this NVHL-related hypofrontality was associated with an abnormal *increase* in gene expression in the dorsal striatum (CA-PU) consistent with the abnormal *increase* in cocaine-induced neuronal activation in the dorsal striatum of NVHL rats observed in Study #2. At the same time, in terms of drug history–induced effects observed in Study #3, cocaine history had its strongest effect in abnormally upregulating gene expression in the dorsal striatum (CA-PU), which again was consistent with how this drug history pathologically increased acute cocaine-induced neuronal activation in the dorsal striatum, as seen in Study #2.

Taken together, these three studies indicate that mental illness–induced acceleration of the addiction disease processes is happening:

(1) *Within cortical–striatal networks* in microcircuits that are postsynaptic to (a) DA projections from the VTA that regulate motivational learning, involving (b) glutamate projections from limbic regions (PFC, AMY, vHCF) that are crucial to generating normal motivational representations in the NAC/ventral striatum, and are pathologically altered in the context of mental illness; and

(2) *Via involuntary biological mechanisms of disease amplification* where mental illness–related abnormalities of cortical–striatal circuity exacerbate and compound with the pathogenic neuroplastic effects of chronic addictive drug delivery in these same circuits that govern motivated behavior.

Addiction is thus installed on neurobiological, neurocomputational, and behavioral levels more efficiently and with greater severity in the context of mental illness. This disease interaction (and major form of addiction vulnerability) occurs neither as a matter of individual choice nor for the medicinal benefit of the individual. Instead, it is a consequence of overlapping neural mechanisms and brain architectures subserving motivational processing, and neuroplasticity, where the pathologies of addiction and mental illness are biophysically convergent and synergistic. Studies 1, 2, and 3, taken together with many other lines of dual-diagnosis–focused neuroscience (spanning animal modeling, neural network simulations, human neuroimaging, and clinical–epidemiological studies), can allow us to succinctly illustrate the integrative neuroscience of addiction pathogenesis (Figure 4.3), and mental illness–based addiction vulnerability and acceleration (Figure 4.4).

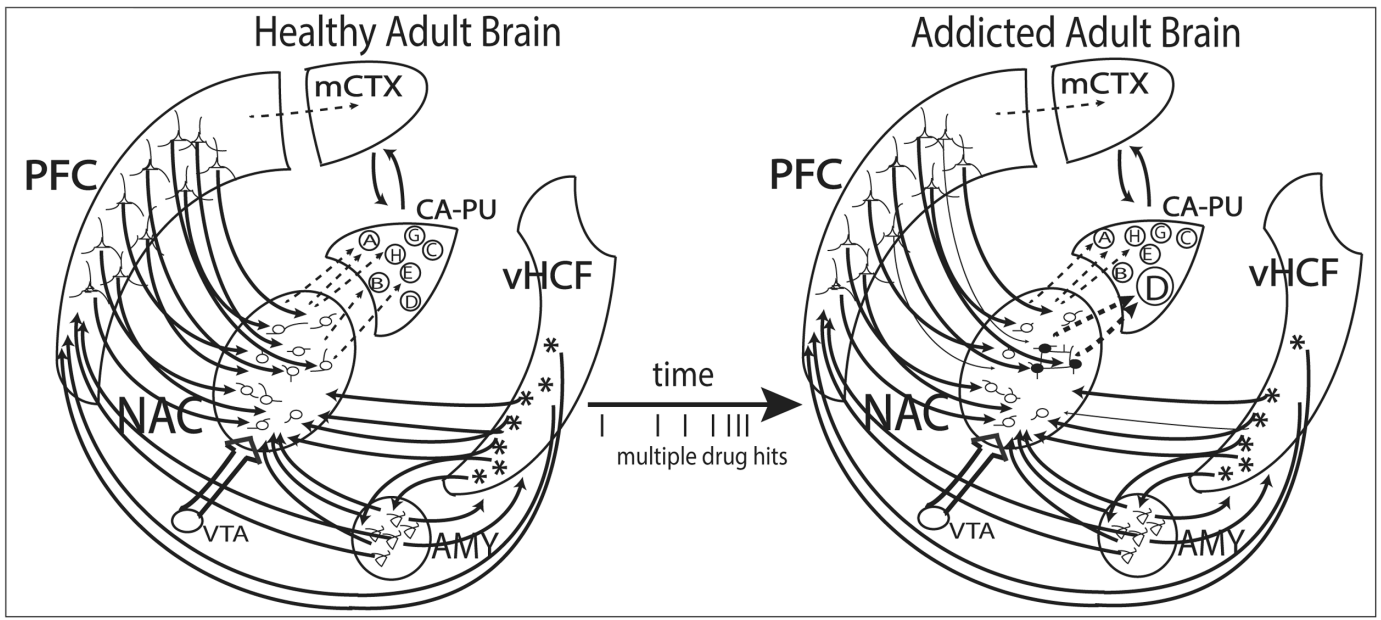
Healthy Adult Brain
mCTX
PFC
CA-PU
vHCF
NAC
VTA
AMY
time
multiple drug hits
Addicted Adult Brain
mCTX
PFC
CA-PU
vHCF
NAC
VTA
AMY

Figure 4.3 Addiction pathogenesis: healthy adult brain. In the *healthy adult brain*, axonal fibers from the prefrontal cortex (PFC), ventral hippocampus (vHCF), and amygdala (AMY) are convergent into the nucleus accumbens (NAC) where they participate in the generation of motivational representations. Dopamine (DA) signaling (large open arrow) from the ventral tegmental area (VTA) into the NAC facilitates transitions between motivational representations as well as mediating neuroplastic changes within the NAC network, allowing motivations to adapt, grow, or newly form. These motivational representations, via polysynaptic pathways (involving "spiraling" relays; thin, stippled arrows from NAC/PFC into the dorsal striatum/caudate putamen (CA-PU) and motor cortical (mCTX) circuits) influence the selection, prioritization, ordering, and formation of specific motor programs represented and stored in the CA-PU network (e.g., as represented as A, B, C, D, E, H, G neuronal firing ensembles in CA-PU). In the addiction disease process, leading to an *addicted adult brain*, multiple drug hits pharmacologically induce abnormal patterns and levels of DA efflux into the NAC network. These episodes of drug-induced DA release produce abnormal incremental neuroplastic changes in the NAC network, leading to the recruitment of NAC neurons (dark-shaded NAC neurons) that represent (encode) strong motivation to acquire and use the drug again. The introduction and growth of this drug-use motivation increases the selection and prioritization of motor programs (behaviors) that subserve drug use, as represented symbolically by the relative growth in size of the drug use behavioral ensemble (D) in CA-PU. This new bout of drug use, in turn, reintroduces even more drug-induced/DA-invoked neuroplastic change to increase drug-use motivation even further, contributing to an escalating, vicious cycle of drug use behavior (more frequent/higher doses) that occurs increasingly beyond willful control.

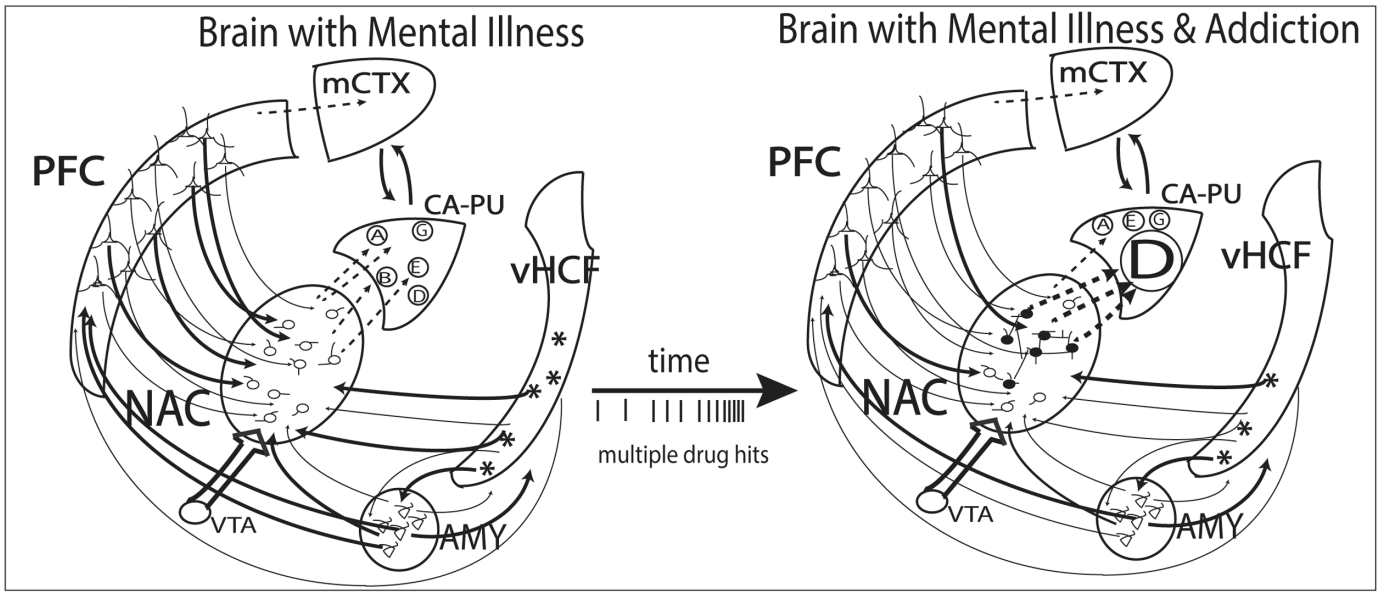
Brain with Mental Illness
mCTX
PFC
CA-PU
A
G
B
E
D
vHCF
NAC
VTA
AMY
time
multiple drug hits
Brain with Mental Illness & Addiction
mCTX
PFC
CA-PU
A
E
G
D
vHCF
NAC
VTA
AMY

Figure 4.4 Addiction pathogenesis accelerated: disease acquisition in mental illness. In the *brain with mental illness* prior to addictive drug exposure, there is a relative impoverishment of long-range network connectivity across frontal cortical–striatal and temporal limbic networks. This impoverishment may take the form of impaired functionality or efficiency of information transfer, reception, or representation between and within subnetworks, and/or relative losses in neuroplasticity (i.e., impairments of adaptability of axo-dendritic connection strengths underpinning learning and memory). Depending on the type and severity of mental illness, different interlimbic connection pathways (e.g., connecting PFC, NAC, AMY, vHCF) and their local networks may be differentially altered. Here, a brain with a severe form of mental illness such as schizophrenia, which carries particularly high levels of addiction risk, is depicted. Fewer functional projections from (i) PFC to NAC; (ii) vHCF to PFC; (iii) vHCF to NAC; and (iv) bidirectionally, between AMY and vHCF are depicted as a thinning and attrition of connections through these pathways. In the hippocampus, with severe mental illness, loss of connectivity and capacity for adaptive neuroplastic change may also be reflected in the loss of neurogenic neurons or dysregulated neuronal turnover (depicted by fewer $*$ symbols in the vHCF). Global connectivity impoverishment also corresponds to thinning of PFC and vHCF layers shown here (which in real brains are detectable by post-mortem or *in vivo* structural neuroimaging studies across most major forms of psychotic, mood, and trauma-related mental illnesses). Note that the NAC network is shown with a subtle loss of intranetwork connectivity, reflecting (and resulting from) the loss of input connectivity from outlying PFC, vHCF, and AMY regions. Accordingly, there are impairments of motivational prioritization, selection or generation of certain motor program sets and sequences stored in the CA-PU (A, B, D, E, G), resulting in a relative loss of storage or functionality of natural adaptative behavioral program representations (shown as loss of C and H motor program sets compared to the healthy brain; Figure 4.3). Note that reflecting these impairments in the motivational-behavioral repertoire, we observe social and occupational dysfunction as hallmark features and criteria for major mental illness diagnoses. Altogether, these conditions are ripe for a more severe and accelerated form of addiction pathogenesis, as shown in the *brain with mental illness and addiction*. In mental illness, the capacity of addictive drug-induced DA release to invoke substantial neuroplastic change within the NAC (needed to install and support drug motivation) is largely preserved, even as the capacity of natural experiences and complex reinforcers to generate and entrain healthy motivation (via natural plasticity) is relatively compromised (as a result of PFC–vHCF, PFC–NAC, and vHCF–NAC connectivity impoverishment). Thus, in mental illness, the balance of motivational entrainment that addictive drugs versus natural reinforcers produce is shifted in the favor of drugs. So, fewer initial drug hits are needed to initiate the addiction cycle, resulting in a more rapidly accelerating and devastatingly compulsive pattern of drug use. Within the NAC of the mentally ill brain, neural ensembles (more interconnected dark neurons) dedicated to representing motivation to acquire and use addictive drugs are more efficiently recruited, further compromising already deficient natural-adaptive motivational representations. At the level of the CA-PU, behavior program sets subserving drug use and taking (D) become so highly prioritized, habitual, and dominating that the already diminished behavioral repertoire (behavioral sets A, B, E, G) are further damaged, even to the point where some adaptive-healthy behavioral sets (e.g., B) are totally lost. In this way, drug-seeking and drug-taking behavior (D) has grown more rapidly, into a more massively oversized, dangerous, and self-reinforcing "tumor" within the behavioral repertoire, compared to what takes place in a brain that is initially relatively free of mental illness. On top of these changes, the various distributed neurotoxic and vascular effects of chronic/heavy drug use in severe addiction cause further deterioration of connectivity and neuroplasticity of the mentally ill brain (as shown by further thinning of PFC–NAC and vHCF–NAC connectivity), and even greater loss of neurogenic neurons ($*$ symbols) in the vHCF. Thus, the heavy addiction comorbidity exacerbates (not self-medicates) the underling mental illness, producing a bidirectional worsening of disease components in dual-diagnosis disorders.

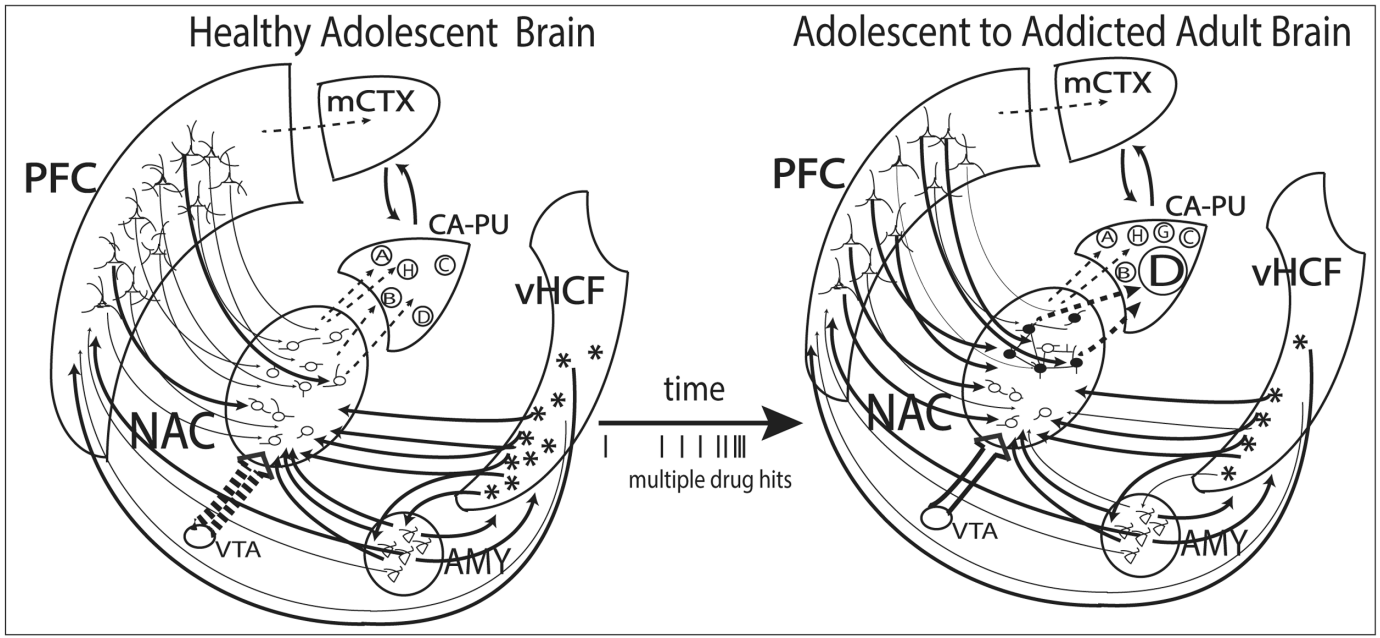
Healthy Adolescent Brain
Adolescent to Addicted Adult Brain
mCTX
PFC
CA-PU
vHCF
NAC
VTA
AMY
time
multiple drug hits
D

Figure 4.5 Addiction pathogenesis accelerated: disease acquisition in adolescent neurodevelopment. In the *healthy adolescent brain*, the PFC, one of the last regions of the brain to mature before full adulthood, is still undergoing substantial neurodevelopment remodeling. On a microarchitectural level, there is an overabundance of local connectivity left over from childhood (symbolized as greater dendritic arborization on PFC neurons). As the brain enters adulthood this excess local connectivity is "pruned" out, in the interest of growth and maturation of longer-range connectivity (e.g., PFC–NAC and PFC with vHCF/AMY networks). This pruning is detectible in neuroimaging as maturational thinning of PFC layers relative to white matter thickening (carrying interregional projection axons from the PFC). Cognitively, these changes to PFC systems correspond to acquisition of more abstract thinking and progressive refinements in the capacity to inhibit (deprioritize or deselect) strong motivations. Subcortically, in the NAC, new motivational representational sets are being installed corresponding to cognitive, sexual, and social maturation involving PFC, AMY, vHCF systems (which project directly into the NAC) and many other subcortical centers including the hypothalamus (not shown). The subcortical situation in adolescence also encompasses functional hyperresponsivity and robustness of DA signaling into the NAC (shown as large stippled VTA–DA projection arrow into the NAC), which facilitates more rapid shifting between motivational sets, relatively robust motivational sensitivity to novel stimuli, and relatively greater plasticity within the NAC network. Within the HCF, neurogenic activity is also greater (symbolized by a relative abundance of $_{*}$). In concert, these subcortical circuit dynamics facilitate more efficient learning and memory of a rapidly expanding motivational behavioral repertoire that will equip the individual for a variety of adult roles. However, during adolescence (compared to adulthood) there is an imbalance between PFC versus subcortical maturational events in which strong new motivations represented (and facilitated by DA) in the NAC are inadequately inhibited by PFC network modulation and control. This developmental state is a double-edged sword: it confers increased impulsivity to adolescent motivation (and behavior) while promoting experimental behavior needed to manage new motivations and learn new adult behaviors and roles (note the *healthy adolescent brain,* compared to *the healthy adult brain* (Figure 4.3) does not yet have a normally sized repertoire of motor programs stored in the CA-PU). Because the healthy adolescent brain is more attracted to novelty (trying new things), the adolescent is more likely to initiate experimentation with addictive drugs. At the same time, due to the aforementioned imbalance involving relatively deficient inhibitory control (PFC) in the face of a relatively robust motivational sensitivity to novelty and neuroplastic change (DA-NAC), the healthy adolescent brain is especially primed to acquiring addiction. With an accumulation of drug hits, the *adolescent to adult addicted brain* is especially sensitive to acquiring drug-use motivation and behavioral patterns, as fortified by the ongoing maturation of the PFC–NAC network assembly during drug usage. As symbolized by the formation of the relatively larger ensemble of dark NAC neurons recruited to represent drug motivation, a larger portion of the representational space in the CA-PU subserving motor programs dedicated to acquiring and using drugs (D) is installed, selected for, and prioritized, even as some new motor programs (G) do come online, whereas others (E) never make it due to developmental disruption caused by the addiction.

Addiction as a Neurodevelopmental Disorder: Adolescent-Brain Amplification of Addiction Vulnerability

Equipped with this neural systems understanding of addiction acceleration by mental illness, it becomes straightforward to understand the neuroscience of addiction vulnerability in another major risk context: *adolescent neurodevelopment*. As in the brain context of mental illness, adolescent neurodevelopment confers heightened vulnerability to the reinforcing effects of addictive drugs so that they are essentially more pharmacologically capable of producing impactful, long-term motivational effects.

Up until about the turn of the century (circa 2000), addiction had been almost exclusively thought of as a disorder of adulthood. This view was reinforced by the fact that by far, most patients in treatment for addiction were older adults, and the chronic accumulating effects of drug addiction on the mind and body (that are part of making an addiction diagnosis) typically take years to fully manifest, well into adulthood. However, a seminal epidemiologic study by Wagner et al. (*Neuropsychopharmacology*, 2002) examining the typical age ranges of drug experimentation and subsequent acquisition of addictions showed that most addictions (regardless of drug type) begin by late adolescence or early adult hood (<age 25). In fact, as a rule of thumb that "averages" the findings across several studies, about 95% of adults with an addiction have their first exposure to the drug before the age of 25, and nearly half of addictions may reach thresholds of becoming clinically diagnosable by the time people reach the age of 20.

Not only are these trends not drug-specific, but they are not human-specific! Rodent models of addiction (variously involving cocaine, nicotine, and alcohol) have also confirmed that when researchers hold the amounts and chronic durations of addictive drug delivery constant, adolescent exposures to the drugs produce greater frequencies and severities of addicted phenotypes in the population compared to adult exposures. Additionally, rodent models of addiction that involve sustained peri-adolescent exposures to drugs have shown that the behavioral expression of the addicted phenotype becomes more robustly expressed as animals progress from adolescence into young adulthood.

Notably, again, not only are the adolescent developmental trends in addiction vulnerability not drug-specific, but they extend even to the developmental onset of *behavioral addictions (that don't involve substances)* such as pathological gambling. Conversely, we observe in human studies that experimentation with addictive drugs happening later in adult life (>25 years) carries significantly *lower* risk of producing addiction than what similar patterns of exposure can in adolescence. Taken together, these lines of data provide quite overwhelming evidence that brain changes that underline the transformation of a child into an adult impart developmentally specific and quite potent effects, amplifying addiction vulnerability in a way that is not drug-specific. Also, these developmental dynamics of addiction risk are so strong that they rise to clinical relevance even when evaluating individual patients: *one important way of assessing severity of addiction in the initial interview of an adult is to determine how early in adolescence their first experimentation and regular use of various substances took place.*

Similar to how we can understand the involuntary nature of mental illness–induced addiction vulnerability, we can understand adolescence-induced addiction vulnerability by appreciating that (a) addiction is a brain disease, with an anatomical and neuropathological basis, and (b) the risk condition (e.g., adolescent neurodevelopment) is itself a special neurobiological circumstance (a stage of neurobiological and anatomical revision) that involves motivational neurocircuitry where addiction strikes hardest. However, unlike the situation with mental illness, adolescent neurodevelopment is *a normal, necessary, and largely adaptive* phase of brain change that nevertheless makes the individual more vulnerable – at least for a few years – to addiction disease. So, while addiction disease opportunistically exploits the presence of another brain disease in the circumstance of mental illness, it can also exploit an otherwise healthy neurobiological context (or transition) in the situation of adolescence. Interestingly, this happens in large part because of the way this developmental stage transiently mimics, both behaviorally and neurobiologically, certain features of mental illness.

Normal adolescent neurodevelopment involves the transient emergence of (or relatively heightened expression of) two major behavioral motifs: (1) **impulsivity** (i.e., behavioral actions conducted despite heightened risk of adverse consequences of the action), and (2) **novelty seeking** (intense interest in exploring and/or engaging in new adult situations and

behaviors). The reader will by now, based on what we have covered in this and prior chapters, recognize these two traits as being general risk indicators for addiction (and also representing endophenotypes, as reviewed above, present in several forms of mental illness). However, in adolescence, although these traits may be risky, they are not pathological. In adolescence, these traits are healthy and functionally necessary because they allow the older child to learn how to think, act, and be motivated like an adult, through actual *behavioral experimentation*, where there is actual physical feedback and consequences of their actions rebounding on them from the external world. This contrasts with the learning style (about the adult world) used by younger children that happens via fantasy and imaginative play, where results and consequences of actions are mostly simulated in the mind and play zone through pretending. So, while the 5-year-old is motivated to play with little toy cars, the 15-year-old is motivated to drive real ones that weigh 2 tons and are capable of going 90 miles an hour. In adolescence, the often quite strong motivation to drive a car is there as a necessity, because obviously, without actually trying to drive, one cannot really learn to drive. The desire to drive is necessary to allow the adolescent to acquire the skill of driving, and to acquire the experience needed to make it safer for them. However, this strong desire is there before years of experience driving have accumulated, necessary for making it relatively safe to drive! In other words, adolescence is *necessarily* a relatively dangerous phase of development, in which exuberant risk-taking (behavioral impulsivity) and the desire to experience new behaviors and stimuli (novelty seeking) is particularly intense – all as an unavoidable requirement for learning how to behave and be motivated as a well-functioning adult. In the example of automobile driving, this risk reality is born out in real numbers: although car accidents are among the leading causes of injuries and death for people between the ages of 16 and 26, they are also by far more likely to happen in this age range than in any other decade of life.

So, in adolescence, the brain is undergoing a deliberate and biologically programmed transition in which heightened impulsivity and novelty-seeking traits are conjoined to motivate behaviors that provide "on the job" learning about functioning in the adult world – all in a physically interactive, relatively risky format, that just cannot happen any other

way. Neurobiologically (returning to an automobile analogy) this developmental epoch can be understood as the brain entering a phase where the ability to put the "brakes on behavior" are relatively weak and underdeveloped or "under construction" (corresponding to heightened impulsivity), while the "accelerator pedal" is operating relatively robustly and in a mode that is tilted toward "go" (corresponding to heightened novelty-seeking). Because we know quite a bit about what parts of the motivational neurocircuitry subserve these somewhat opposing functions of impulse control (in the case of the PFC) versus novelty motivation (in the case of subcortical motivational–limbic systems including VTA–DA, NAC, AMY, and vHCF systems) – we know where to look in the brain to see how adolescent neurodevelopment is producing functional changes in these structures to increase addiction risk. So again, as in the general example of mental illness that encompasses behavioral impulsivity and PFC dysfunction (as per the example of the NVHL modeling discussed above), we see a similar kind of impulsivity–PFC dysfunction motif associating with addiction vulnerability again, but this time in the context of adolescent neurodevelopmental change.

Essentially, in adolescence, the PFC is undergoing a major phase of neurobiological remodeling where local neural connectivity is being significantly reduced while longer-range intercortical and cortical–limbic connections are growing stronger. This corresponds to heightened levels of **synaptic pruning** observable on the cellular level in the PFC, and **PFC volume reductions** observable on the gross/neuroimaging level (and many other microcircuit changes not discussed here). Concurrent with this remodeling, the PFC is not fully able to effectively inhibit or regulate motivations represented in the NAC that are capable of driving behavior. Hence, the adolescent is more impulsive. At the same time, changes in AMY and vHCF subcircuits, and changes in their connectivity and communications with the NAC, are facilitating the emergence of adult motivations in the NAC (e.g., pertaining to sexual behavior, social relationships, and other adult behaviors and occupations). With this subcortical revision of limbic circuits, we also see evidence that the DA neurotransmitter system, which regulates the gating, flow, and neuroplastic revision of the NAC network, is operating in a relatively robust functional state. Evidence for greater pre- and postsynaptic sensitivity and reactivity of the DA system in the NAC emerges alongside a relatively heightened state of neuroplastic flexibility in prefrontal cortical–

ventral striatal circuits, and capacity for long-term storage of novel neural representations in these systems that will make up the individual's adult motivational-behavioral repertoire. In this way, the adolescent brain is primed with neurobiological attributes that transiently make the brain: (1) more likely to be exposed to (experiment with) a wide variety of addictive drugs (associated with PFC-based structural remodeling and impulsivity); (2) more susceptible to the short-term reinforcing effects of addictive drugs (from DA–NAC system-based hyperreactivity corresponding to heightened novelty sensitivity); and (3) more susceptible to the long-term motivational effects of addictive drugs (from a combination of PFC and NAC network-based elevations in neuroplastic flexibility that is susceptible to DA-mediated neuroplastic revision).

As illustrated in Figure 4.5, which summarizes this neurobiology of adolescent addiction vulnerability, there are certain parallels and themes shared with what's happening in the neurobiology of mental illness–based addiction vulnerability (compare with Figure 4.4). Indeed, in viewing these figures, it should be appreciated that (1) adolescent-age vulnerability to addiction pathogenesis and (2) the emergence of an adolescent-onset mental illness, which also contributes to addiction vulnerability, are not mutually exclusive brain contexts and may happen at the same time in particularly vulnerable individuals. And, consistent with an interactive effect of these two often compounding vulnerability states, we note that many of the major mental illnesses that impart some of the greatest addiction risk (e.g., schizophrenia, bipolar disorder, PTSD, personality disorders, and so on) also tend to be diagnoses that typically show peri-adolescent and/or young adult onset or worsening. When considering that different forms of severe adult mental illnesses can be understood as representing various states of arrested development occurring in certain limbic regions (in the process of the adolescent brain turning into an adult brain), it is also possible to understand mental illness–based addiction vulnerability as being quite similar to that of adolescent neurodevelopment, albeit manifesting in a much longer-lasting and more severe form of vulnerability. Notably, however, it is important to keep in mind that adolescent neurodevelopment is not a mental illness (as much as parents of teenage children may sometimes feel that it is!). Different types of mental illness reflect different patterns and anatomical distributions of neural network abnormalities (spanning PFC, NAC, AMY, vHCF subcircuits and other regions), and these illness forms are generated by differential

combinations of polygenetic factors and differential timing of adverse environmental experiences. In the case of adolescent neurodevelopment, we are describing a much more orderly, normal, and genetically staged unfolding of cortical–limbic maturation, in which the PFC becomes the last large neural network to wire in as an adult system. But still, because the AMY and vHCF project directly into the PFC (and NAC), mental illness-based abnormalities that are primarily "seated" in the AMY or vHCF may have downstream effects on PFC anatomy and function that only become fully manifest as the individual goes through peri-adolescent maturation of the PFC. So, much as different forms of adult mental illness may represent impaired forms of neuroplasticity in different limbic subcircuits, creating a clinical state of adulthood that is like being stuck in a prolonged adolescence, mental illness and adolescent neurodevelopment can interactively change addiction thresholds and probabilities of acquiring addictions that become quite severe and involve multiple substances. In summary, adolescent neurodevelopment and mental illness both operate as **cross-sensitization** and **brain attractor states** for the acquisition of addictions.

Pathological Rebound of Addiction to Worsen Mental Illness

Adding even greater complexity to these frequently interactive neurobiological dynamics occurring between adolescent neurodevelopment and mental illness (to increase addiction vulnerability) is the concurrent accumulating impact of chronic, heavy substance use (that happens only in addiction) to produce toxic effects on brain neurocircuitry and neuroplasticity. Basically, the addiction itself, even when brought on by adolescent age or mental illness vulnerability factors, also rebounds biologically to (a) prolong or impair adolescent neurodevelopmental change, and (b) compound/worsen the already existing biology of an underlying mental illness. Thus, most addictive drugs including alcohol, nicotine, opioids, cannabinoids, stimulants, and so on, when taken chronically and in heavy doses (in addiction patterns) in the adolescent or adult brain, can exert a range of adverse effects on brain circuits and neuroplasticity that subserves cognition, emotion, social interactions, decision-making, and (of course) motivation. So,

this rebounding toxicology of addictive patterns of drug use actually worsens mental illness, occurring concurrent with the biological effect of mental illness to increase addiction risk and severity. This biology underpins the **bidirectional causality** between addiction and mental illness. As mentioned in Chapter 2 (*myth-busters*), this bidirectional causality is strong enough (and scientifically well-supported enough) to explain the close clinical and epidemiological associations between mental illness and addiction, so that there is no need to rely on "self-medication hypotheses" for explaining dual diagnosis, which requires accepting the many logical, empirical, and clinical failures that this hypothesis entails. As we will discuss in Chapter 5, the tight neurobiological connectivity and bidirectional causality that exists between mental illness and addiction is a key focus for the field of addiction psychiatry and its *raison d'etre* for providing expert integrated care for co-occurring disorders.

Although chronic heavy drug use in the context of chronic addiction does worsen mental illness as a rule of thumb, it is important to mention some key caveats to this generalization. First, of course, the severity and quality of the effect depends on which addictive drug type, or combination, or route of use, the patient has been exposed to chronically. The different main addictive drug types do have quite diverse psychoactive and neurotoxicological profiles, involving different intoxicating versus withdrawal effects. They have differential liabilities on cognition, and different mechanisms through which they not only impact the brain but alter the function of other body organs that can also impact the brain. Second, there are many biological pathways and mechanisms by which each addictive drug (through chronic/heavy use) can harm the brain. For example, cocaine and nicotine can each cause hemorrhagic strokes, or they can contribute to hypertension and arterial disease that can lead to ischemic hypoperfusion across different brain regions. Opioids, as in the context of opioid overdose, can also cause a global ischemic brain injury, whereas i.v. use of opioids or amphetamines can lead to endocarditis, that can then lead to embolic strokes in the brain. An alcohol overdose can cause an ischemic brain injury too, whereas the chronic toxicological effects of the drug on neurons and neuronal connectivity can cause generalized or focal brain atrophy. Too many bouts of alcohol withdrawal can produce seizures that are also, on some level, neurotoxic. Then there is the capacity of addictive drug intoxication, whether involving stimulants or depressants, to make the individual prone to brain injuries resulting from accidents or assaults.

On a more subtle level, most of the addictive drug types and classes (when used chronically) exert pathological effects on neuroplasticity (and learning and memory) in different parts of the brain, which can keep patients stuck in thought or behavioral patterns that are not adaptive to their situation. In these patterns of *being stuck*, patients are less able to effectively meet the challenge of normal life stressors or psychosocial change, and they are also *more* **treatment-refractory** (less able to respond) to evidence-based treatments for mental illness, including both psychotherapies and medication treatments.

A third major variable in the capacity of addictive drug use to generate mental illness symptoms or syndromes (that could be long-lasting) is the developmental timing of the chronic addictive drug exposure (e.g., whether it is happening in adolescence, early adulthood, or older age). Each of these brain ages, of course, encompass different neurobiological and neural network attributes, so the brain substrates upon which the toxic or cardiovascular effects of additive drugs exact a cost vary by age. Focusing again on adolescence, we note that although the brain may be more plastic (capable of neural network remodeling associated with learning and memory) compared to older adult ages, it is also more potentially alterable by the long-term neuroplastic effects of addictive drugs, as previously reviewed. Moreover, adolescence and young adulthood are ages when the brain needs to be highly motivated to learn about the world, adult occupations, and social pursuits, in a way that (hopefully) are unimpeded by either the adverse motivational or cognitive effects of addictive drugs. The adolescent brain is highly sensitive to the cognitive effects of addictive drugs to disrupt educational obtainment, their motivational effects to derail academic effort and achievement, and their social-motivational effects in causing preference for friends based on whether they use drugs as well.

Impaired Hippocampal Neurogenesis in the Bidirectional Causality of Mental illness and Addiction

Accumulative neurotoxic damage resulting from additive patterns of chronic drug use can be observed in the brain in several ways, all of which can mimic what endogenous mental illness entails. We have already covered two of these motifs: (1) cortical–limbic atrophy (e.g., subtle shrinkage of PFC, AMY, vHCF, or associated regions, visible in **structural neuroimaging**) and (2)

microstructural or functional evidence of loss of connectivity within or between these cortical–limbic regions (visible by histopathological analysis and functional neuroimaging). A third neurotoxic motif involved in the bidirectional pathogenesis of dual diagnosis involves **hippocampal neurogenesis**. Neurogenesis is a type of neuroplasticity that occurs at particularly high rates in certain parts of the brain (e.g., in the **dentate gyrus** sector of the HCF), where new neurons are born and "wire in" to the local neural network at particularly high rates. This neuronal regeneration is also accompanied by a removal of older neurons – a death rate – and it persists well into adulthood and older age. As part of a continual process of hippocampal neuronal turnover and population renewal, neurogenesis likely endows the hippocampal network with a more robust mechanism for neuroplastic change compared to that allowed by typical axo-dendritic synaptic plasticity. By analogy, demolishing a whole building and constructing a new one in its place is a more profound change than simply remodeling the interior or adding a room.

Hippocampal neurogenesis appears to be dynamic over time in mammals depending on the degree and durations of environmental changes, stressors, and related cognitive challenges they encounter. Interestingly, although the appropriate regulation of neurogenesis and neuronal turnover may be important to maintaining resilience against a range of stress-exacerbated psychiatric disorders such as major depression and PTSD, it has also been shown that psychiatric treatments including antidepressants, ECT (**electroconvulsive therapy**), and even cardiovascular exercise can upregulate neurogenesis. At the same time, as a rule of thumb, most addictive drug classes have been shown to *suppress hippocampal neurogenesis*, mimicking what endogenous mental illness may do. This evidence, taken alongside animal modeling studies demonstrating the effects of developmental damage to the vHCF (as in the NVHL model) in generating *both mental illness and addiction vulnerability*, suggests that dysregulated or impaired hippocampal neurogenesis is involved in both mental illness and elevated addiction risk. At the same time, the chronic use of addictive drugs, which addiction would create, would in turn further suppress hippocampal neurogenesis and plasticity, worsening the underlying mental illness.

In summary of this chapter, we have reviewed how many causal ingredients and neural mechanisms of addiction risk spanning genetics, adverse environmental experiences, mental illness, and adolescent

neurodevelopment can operate independently or in concert to elevate addiction risk. In turn, severe chronic addictions can then rebound in very complex ways to intensify all of these risk factors – especially mental illness – within individuals or, intergenerationally, within families. For example, the genetic loading of addiction risk can be concentrated intergenerationally, given the phenomena that people with severe active addictions are more likely to have sexual relations and procreate with others with severe active addictions, thus concentrating genetic risk in their offspring. At the same time, the increased likelihood of both parents suffering with severe addictions when one parent does translates not only into a greater genetic loading for mental illness, but greater probability of exposure to a variety of addictive drugs at a younger age in the offspring, and a greater risk of children suffering from socioeconomic deprivations, educational failures, traumatic experiences, and attachment failures, which all raise the risk of both mental illness and addiction in adulthood (see Figure 1.2). As we will describe in the final chapter of this book, which focuses on diagnosis and treatment, it is for this reason that addiction psychiatry puts a premium on, and is best equipped for, providing expert, integrated prevention and treatment of addiction and co-occurring mental disorders.

BIBLIOGRAPHY

Barnett, J. H., U. Werners, S. M. Secher, K. E. Hill, R. Brazil, K. Masson, D. E. Pernet, J. B. Kirkbride, G. K. Murray, E. T. Bullmore, and P. B. Jones. 2007. Substance use in a population-based clinic sample of people with first-episode psychosis. *Br J Psychiatry*, 190: 515–20.

Bechara, A. 2003. Risky business: Emotion, decision-making and addiction. *J Gambl Stud*, 19: 23–51.

Becker, J. B., M. L. McClellan, and B. G. Reed. 2017. Sex differences, gender and addiction. *J Neurosci Res*, 95: 136–47.

Bell, R. L., Z. A. Rodd, L. Lumeng, J. M. Murphy, and W. J. McBride. 2006. The alcohol-preferring P rat and animal models of excessive alcohol drinking. *Addict Biol*, 11: 270–88.

Berg, S. A., and R. A. Chambers. 2008. Accentuated behavioral sensitization to nicotine in the neonatal ventral hippocampal lesion model of schizophrenia. *Neuropharmacology*, 54: 1201–07.

Berg, S. A., C. L. Czachowski, and R. A. Chambers. 2011. Alcohol seeking and consumption in the NVHL neurodevelopmental rat model of schizophrenia. *Behav Brain Res*, 218: 346–49.

Berg, S. A., A. M. Sentir, R. L. Bell, E. A. Engleman, and R. A. Chambers. 2015. Nicotine effects in adolescence and adulthood on cognition and alpha(4)beta (2)-nicotinic receptors in the neonatal ventral hippocampal lesion rat model of schizophrenia. *Psychopharmacology*, 232: 1681–92.

Berg, S. A., A. M. Sentir, B. S. Cooley, E. A. Engleman, and R. A. Chambers. 2014. Nicotine is more addictive, not more cognitively therapeutic in a neurodevelopmental model of schizophrenia produced by neonatal ventral hippocampal lesions. *Addict Biol*, 19: 1020–31.

Bickel, W. K., L. Green, and R. E. Vuchinich. 1995. Behavioral economics. *J Exp Anal Behav*, 64: 257–62.

Boscarino, J. A., M. Rukstalis, S. N. Hoffman, J. J. Han, P. M. Erlich, G. S. Gerhard, and W. F. Stewart. 2010. Risk factors for drug dependence among out-patients on opioid therapy in a large US health-care system. *Addiction*, 105: 1776–82.

Bracken, A. L., R. A. Chambers, S. A. Berg, Z. A. Rodd, and W. J. McBride. 2011. Nicotine exposure during adolescence enhances behavioral sensitivity to nicotine during adulthood in Wistar rats. *Pharmacol Biochem Behav*, 99: 87–93.

Brady, A. M., S. E. McCallum, S. D. Glick, and P. O' Donnell. 2008. Enhanced methamphetamine self-administration in a neurodevelopmental rat model of schizophrenia. *Pschopharmacology*, 200: 205–15.

Brewer, J. A., and M. N. Potenza. 2007. The neurobiology and genetics of impulse control disorders: Relationships to drug addictions. *Biochem Pharmacol*, 75: 63–75.

Burns, L. H., L. Annett, B. J. Everett, T. W. Robbins, and A. E. Kelley. 1996. Effects of lesions to amygdala, ventral subiculum, medial prefrontal cortex, and nucleus accumbens on the reaction to novelty: Implication for limbic–striatal interactions. *Behav Neurosci*, 110: 60–73.

Chambers, J. 2017. The neurobiology of attachment: From infancy to clinical outcomes. *Psychodyn Psychiatry*, 45: 542–63.

Chambers, R. A., and S. K. Conroy. 2007. Network modeling of adult neurogenesis: Shifting rates of neuronal turnover optimally gears network learning according to novelty gradient. *J Cogn Neurosci*, 19: 1–12.

Chambers, R. A., R. M. Jones, S. Brown, and J. R. Taylor. 2005. Natural reward related learning in rats with neonatal ventral hippocampal lesions and prior cocaine exposure. *Psychopharmacology*, 179: 470–78.

Chambers, R. A., J. K. Krystal, and D. W. Self. 2001. A neurobiological basis for substance abuse comorbidity in schizophrenia. *Biol Psychiatry*, 50: 71–83.

Chambers, R. A., and M. N. Potenza. 2003. Neurodevelopment, impulsivity, and adolescent gambling. *J Gambl Stud*, 19: 53–84.

Chambers, R. A., M. N. Potenza, R. E. Hoffman, and W. Miranker. 2004. Simulated apoptosis/neurogenesis regulates learning and memory capabilities of adaptive neural networks. *Neuropsychopharmacology*, 29: 747–58.

Chambers, R. A., T. J. Sajdyk, S. K. Conroy, J. E. Lafuze, S. D. Fitz, and A. Shekhar. 2007. Neonatal amygdala lesions: Co-occurring impact on social/fear-related behavior and cocaine sensitization in adult rats. *Behav Neurosci*, 121: 1316–27.

Chambers, R. A., and D. W. Self. 2002. Motivational responses to natural and drug rewards in rats with neonatal ventral hippocampal lesions: An animal model of dual diagnosis schizophrenia. *Neuropsychopharmacology*, 27: 889–905.

Chambers, R. A., A. M. Sentir, and E. A. Engleman. 2010. Ventral and dorsal striatal dopamine efflux and behavior in rats with simple vs. co-morbid histories of cocaine sensitization and neonatal ventral hippocampal lesions. *Pschopharmacology*, 212: 73–83.

Chambers, R. A., T. Sheehan, and J. R. Taylor. 2004. Locomotor sensitization to cocaine in rats with olfactory bulbectomy. *Synapse*, 52: 167–75.

Chambers, R. A., and J. R. Taylor. 2004. Animal modeling dual diagnosis schizophrenia: Sensitization to cocaine in rats with neonatal ventral hippocampal lesions. *Biol Psychiatry*, 56: 308–16.

Chambers, R. A., J. R. Taylor, and M. N. Potenza. 2003. Developmental neurocircuitry of motivation in adolescence: A critical period of addiction vulnerability. *Am J Psychiatry*, 160: 1041–52.

Chambers, R. A. 2013. Adult hippocampal neurogenesis in the pathogenesis of addiction and dual diagnosis disorders. *Drug Alcohol Depend*, 130: 1–12.

Chambers, R. A., J. N. McClintick, A. M. Sentir, S. A. Berg, M. Runyan, K. H. Choi, and H. J. Edenberg. 2013. Cortical–striatal gene expression in neonatal hippocampal lesion (NVHL)-amplified cocaine sensitization. *Genes Brain Behav*, 12: 564–75.

Chambers, R. A., and A. M. Sentir. 2020. Integrated effects of neonatal ventral hippocampal lesions and impoverished social–environmental rearing on endophenotypes of mental illness and addiction vulnerability. *Dev Neurosci*, 41: 263–73.

Chambers, R. A., A. M. Sentir, S. K. Conroy, W. A. Truitt, and A. Shekhar. 2010. Cortical–striatal integration of cocaine history and prefrontal dysfunction in animal modeling of dual diagnosis. *Biol Psychiatry*, 67: 788–92.

Chopra, S., A. Segal, S. Oldham, A. Holmes, K. Sabaroedin, E. R. Orchard, S. M. Francey, B. O'Donoghue, V. Cropley, B. Nelson, J. Graham, L. Baldwin, J. Tiego, H. P. Yuen, K. Allott, M. Alvarez-Jimenez, S. Harrigan, B. D. Fulcher, K. Aquino, C. Pantelis, et al. 2023. Network-based spreading of gray matter changes across different stages of psychosis. *JAMA Psychiatry*, 80: 1246–57.

Cicchetti, D., and F. A. Rogosch. 1996. Equifinality and multifinality in developmental psychopathology. *Dev Psychopathol*, 8: 597–600.

Cicchetti, D., and F. A. Rogosch. 1999. Psychopathology as risk for adolescent substance use disorders: A developmental psychopatholgy perspective. *J Clin Child Psychol*, 28: 355–65.

Conroy, S. K., Z. Rodd, and R. A. Chambers. 2007. Ethanol sensitization in a neurodevelopmental lesion model of schizophrenia in rats. *Pharmacol Biochem Behav*, 86: 386–94.

Erickson, C. A., and R. A. Chambers. 2006. Male adolescence: Neurodevelopment and behavioral impulsivity. in J. Grant and M. N. Potenza (eds.), *Textbook of Men's Mental Health*. Washington, DC: American Psychiatric Publishing.

Esterlis, I., M. Ranganathan, F. Bois, B. Pittman, M. R. Picciotto, L. Shearer, A. Anticevic, J. Carlson, M. J. Niciu, K. P. Cosgrove, and D. C. D'Souza. 2014. In vivo evidence for beta nicotinic acetylcholine receptor subunit upregulation in smokers as compared with nonsmokers with schizophrenia. *Biol Psychiatry*, 76: 495–502.

Goldstein, R. B., S. M. Smith, S. P. Chou, T. D. Saha, J. Jung, H. Zhang, R. P. Pickering, W. J. Ruan, B. Huang, and B. F. Grant. 2016. The epidemiology of DSM-5 posttraumatic stress disorder in the United States: results from the National Epidemiologic Survey on Alcohol and Related Conditions-III. *Soc Psychiatry Psychiatr Epidemiol*, 51: 1137–48.

Grant, B. F., T. D. Saha, W. J. Ruan, R. B. Goldstein, S. P. Chou, J. Jung, H. Zhang, S. M. Smith, R. P. Pickering, B. Huang, and D. S. Hasin. 2016. Epidemiology of DSM-5 drug use disorder: Results from the National Epidemiologic Survey on Alcohol and Related Conditions-III. *JAMA Psychiatry*, 73: 39–47.

Groenewegen, H. J., C. I. Wright, A. V. Beijer, and P. Voorn. 1999. Convergence and segregation of ventral striatal inputs and outputs. *Ann N Y Acad Sci*, 877: 49–63.

Hartz, S. M., C. N. Pato, H. Medeiros, P. Cavazos-Rehg, J. L. Sobell, J. A. Knowles, L. J. Bierut, M. T. Pato, and Consortium Genomic Psychiatry Cohort. 2014. Comorbidity of severe psychotic disorders with measures of substance use. *JAMA Psychiatry*, 71: 248–54.

Hatoum, A. S., S. M. Colbert, E. C. Johnson, S. B. Huggett, J. D. Deak, G. Pathak, M. V. Jennings, S. E. Paul, N. R. Karcher, I. Hansen, D. A. A. Baranger, A. Edwards, A. Grotzinger, Substance Use Disorder Working Group of the Psychiatric Genomics Consortium; E. M. Tucker-Drob, H. R. Kranzler, L. K. Davis, S. Sanchez-Roige, R. Polimanti, J. Gelernter, et al. 2023. Multivariate genome-wide association meta-analysis of over 1 million subjects identifies loci underlying multipole substance use disorders. *Nature Mental Health*, 1: 210–23.

Hulvershorn, L. A., C. A. Erickson, and R. A. Chambers. 2010. Impact of childhood mental health problems. In J. E. Grant and M. N. Potenza (eds.), *Young Adult Mental Health*. Oxford: Oxford University Press.

Jeanblanc, J., K. Balguerie, F. Coune, R. Legastelois, V. Jeanblanc, and M. Naassila. 2015. Light alcohol intake during adolescence induces alcohol addiction in a neurodevelopmental model of schizophrenia. *Addict Biol*, 20: 490–99.

Jentsch, J. D., and J. R. Taylor. 1999. Impulsivity resulting from frontostriatal dysfunction in drug abuse: Implications for the control of behavior by reward-related stimuli. *Psychopharmacology*, 146: 373–90.

Kalman, D., S. B. Morrissette, and T. P. George. 2005. Co-morbidity of smoking in patients with psychiatric and substance use disorders. *Am J Addict*, 14: 106–23.

Krieger, H., C. M. Young, A. M. Anthenien, and C. Neighbors. 2018. The epidemiology of binge drinking among college-age individuals in the United States. *Alcohol Res*, 39: 23–30.

Lewis, D. A. 1997. Development of the prefrontal cortex during adolescence: Insights into vulnerable neural circuits in schizophrenia. *Neuropsychopharmacology*, 16: 385–98.

Lipska, B. K., G. E. Jaskiw, and D. R. Weinberger. 1993. Postpubertal emergence of hyperresponsiveness to stress and to amphetamine after neonatal excitotoxic hippocampal damage: A potential animal model of schizophrenia. *Neuropsychopharmacology*, 9: 67–75.

Lopez-Quintero, C., J. Perez de los Cobos, D. S. Hasin, M. Okuda, S. Wang, B. F. Grant, and C. Blanco. 2011. Probability and predictors of transition from first use to dependence on nicotine, alcohol, cannabis, and cocaine: Results of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). *Drug Alcohol Depend*, 115: 120–30.

Masterman, D. L., and J. L. Cummings. 1997. Frontal–subcortical circuits: The anatomical basis of executive, social and motivational behaviors. *J Psychopharmacol*, 11: 107–14.

Mills, K. L., A. L. Goddings, L. S. Clasen, J. N. Giedd, and S. J. Blakemore. 2014. The developmental mismatch in structural brain maturation during adolescence. *Dev Neurosci*, 36: 147–60.

Moffett, M. C., A. Vicentic, M. Kozel, P. Plotsky, D. D. Francis, and M. J. Kuhar. 2007. Maternal separation alters drug intake patterns in adulthood in rats. *Biochem Pharmacol*, 73: 321–30.

O'Donnell, P. 2012. Cortical disinhibition in the neonatal ventral hippocampal lesion model of schizophrenia: New vistas on possible therapeutic approaches. *Pharmacol Ther*, 133: 19–25.

Pennartz, C. M. A., H. J. Groenewegen, and F. H. Lopez da Silva. 1994. The nucleus accumbens as a complex of functionally distinct neuronal ensembles: An integration of behavioral, electrophysiological and anatomical data. *Progr Neurobiol*, 42: 719–61.

Petry, N. M., W. K. Bickel, and M. Arnett. 1998. Shortened time horizons and insensitivity to future consequences in heroin addicts. *Addiction*, 93: 729–38.

Rao, K. N., A. M. Sentir, E. A. Engleman, R. L. Bell, L. A. Hulvershorn, A. Breier, and R. A. Chambers. 2016. Toward early estimation and treatment of addiction vulnerability: Radial arm maze and *N*-acetyl cysteine before cocaine sensitization or nicotine self-administration in neonatal ventral hippocampal lesion rats. *Psychopharmacology*, 233: 3933–45.

Rodd-Henricks, Z. A., R. L. Bell, K. A. Kuc, J. M. Murphy, W. J. McBride, L. Lumeng, and T. K. Li. 2002a. Effects of ethanol exposure on subsequent acquisition and

extinction of ethanol self-administration and expression of alcohol-seeking behavior in adult alcohol-preferring (P) rats: I. Periadolescent exposure. *Alcohol Clin Exp Res*, 26: 1632–41.

Rodd-Henricks, Z. A., R. L. Bell, K. A. Kuc, J. M. Murphy, W. J. McBride, L. Lumeng, and T. K. Li. 2002b. Effects of ethanol exposure on subsequent acquisition and extinction of ethanol self-administration and expression of alcohol-seeking behavior in adult alcohol-preferring (P) rats: II. Adult exposure. *Alcohol Clin Exp Res*, 26: 1642–52.

Schiffer, B., B. W. Muller, N. Scherbaum, M. Forsting, J. Wiltfang, N. Leygraf, and E. R. Gizewski. 2010. Impulsivity-related brain volume deficits in schizophrenia–addiction comorbidity. *Brain*, 133: 3093–103.

Sentir, A. M., R. L. Bell, E. A. Engleman, and R. A. Chambers. 2020. Polysubstance addiction vulnerability in mental illness: Concurrent alcohol and nicotine self-administration in the neurodevelopmental hippocampal lesion rat model of schizophrenia. *Addict Biol*, 25(1): e12704.

Spear, L P. 2000. The adolescent brain and age-related behavioral manifestations. *Neurosci Biobehav Rev*, 24: 417–63.

Spitzer, M. 1999. *The Mind Within the Net*. London: MIT Press.

Szerman, N., and L. Peris. 2014. Personality disorders and addiction disorders. In N. el-Guebaly, G. Carra, and M. Galanter (eds.), *Textbook of Addiction Treatment International Perspective*. Milan: Springer-Verlag Italia.

Teicher, M. H., and J. A. Samson. 2013. Childhood maltreatment and psychopathology: A case for ecophenotypic variants as clinically and neurobiologically distinct subtypes. *Am J Psychiatry*, 170: 1114–33.

Teicher, M. H., J. A. Samson, C. M. Anderson, and K. Ohashi. 2016. The effects of childhood maltreatment on brain structure, function and connectivity. *Nat Rev Neurosci*, 17: 652–66.

Tseng, K. Y., R. A. Chambers, and B. K. Lipska. 2009. The neonatal ventral hippocampal lesion as a heuristic neurodevelopmental model of schizophrenia. *Behav Brain Res*, 204: 295–305.

Tseng, K. Y., B. L. Lewis, T. Hashimoto, S. R. Sesack, M. Kloc, D. A. Lewis, and P. O'Donnell. 2008. A neonatal ventral hippocampal lesion causes functional deficits in adult prefrontal cortical interneurons. *J Neurosci*, 28: 12691–99.

Tseng, K. Y., B. L. Lewis, B. K. Lipska, and P. O'Donnell. 2007. Post-pubertal disruption of medial prefrontal cortical dopamine–glutamate interactions in a developmental animal model of schizophrenia. *Biol Psychiatry*, 62: 730–38.

Van Dam, N. T., K. Rando, M. N. Potenza, K. Tuit, and R. Sinha. 2014. Childhood maltreatment, altered limbic neurobiology, and substance use relapse severity via trauma-specific reductions in limbic gray matter volume. *JAMA Psychiatry*, 71: 917–25.

Wagner, F. A., and J. C. Anthony. 2002. From first drug use to drug dependence: developmental periods of risk for dependence upon marijuana, cocaine, and alcohol. *Neuropsychopharmacology*, 26: 479–88.

Weinberger, D. R. 1999. Cell biology of the hippocampal formation in schizophrenia. *Biol Psychiatry*, 45: 395–402.

Weinberger, D. R., M. S. Aloa, T. E. Goldberg, and K. F. Berman. 1994. The frontal lobes and schizophrenia. *J Neuropsychiatry*, 6: 419–27.

Zarse, E. M., M. R. Neff, R. Yoder, L. Hulvershorn, J. E. Chambers, and R. A. Chambers. 2019. The adverse childhood experiences scale: Two decades of research on childhood trauma as a primary cause of adult mental illness, addiction and medical diseases. *Cogent Medicine*, 6.

Zhang, X., E. A. Stein, and L. E. Hong. 2010. Smoking and schizophrenia independently and additively reduce white matter integrity between striatum and frontal cortex. *Biol Psychiatry*, 68: 674–77.

5

Diagnosis and Treatment: Disease Tracking, Reduction, and Remission

Learning Points

- **Addiction is a chronic waxing and waning brain disease that is etiologically and biologically interactive with mental illness. Addiction psychiatry is a physician-led specialty that provides expert science-based care for patients across the addiction/mental illness comorbidity spectrum**. The 2×4 model is a clinical delivery model that unifies addiction psychiatry neuroscience and physician-led clinical expertise with integrated dual-diagnosis treatment. The 2×4 model rejects fragmented, split care models of behavioral healthcare delivery. It emphasizes team-based care conducted by addiction psychiatrists, nurses, and therapists that integrates diagnostic work, psychotherapies, medication management, and professional communications to provide individualized care for patients across the mental illness/addiction comorbidity spectrum.
- **Diagnostic work in addiction psychiatry attends to both mental illness and addiction-related signs and symptoms with equal prioritization according to individual patient needs. Diagnostic work is not just cross-sectional but longitudinal**

and ongoing to guide initial treatment and track illness evolution and treatment outcomes. Initial and continuous outcome tracking in addiction psychiatry relies on (1) the addiction psychiatry evaluation and exam; (2) drug testing and PDMP (prescription drug monitoring program inquiry); and (3) clinical engagement and collateral input tracking.

- **Treatments in addiction psychiatry are based on a coherent integration of the two main classes of therapeutic interventions: psychotherapeutics and medication strategies**. These modalities should both be available for flexibly targeting mental illness and/or addiction; they can be delivered in sequential or concurrent-integrated schedules in an individualized way depending on each patient's unique circumstances, tolerability, and illness comorbidities.
- **In recovery, patients move across clinical stages of change and may transition through various treatment phases including detoxification and withdrawal treatment (DWT), harm reduction (HR), and full remission (FR) strategies.**
- **New frontiers in addiction psychiatry therapeutics research will encompass the development of novel integrative treatments that combine multiple treatments to target one illness, or one treatment that can target multiple diagnoses**. New integrative techniques that produce more profound (and safe) approaches for changing brain connectivity, plasticity, and architecture (**deep network therapeutics**) at critical transition points in recovery trajectories are expected to provide better preventative and therapeutic effects for both mental illness and addiction diseases.

Introduction

Although addiction is extremely common and very responsive to treatment, most people suffering from the disease are not in or do not have access to adequate, much less excellent, treatment. As of the second decade of the 2000s, even among commercially insured patients who receive emergency room care after a near-lethal overdose, less than 1 in 5 patients receive follow-up care for an addictive disease that is threatening to kill them. For patients suffering with both an addiction and moderate to severe mental

illness (which represents the mainstream sector of all behavioral health patients), less than 1 in 10 receive adequate integrated dual-diagnosis care, where both the addictions and mental illness are treated expertly and concurrently in an integrated way. These statistics point to the still unmet public health need to increase the workforce of addiction psychiatrists and allied professionals who are cross-trained and expertly capable in the diagnosis and treatment of the broad spectrum of patients with addictions, mental illnesses, and their various dual-diagnosis combinations.

Based on initial and ongoing diagnostic assessments, addiction psychiatrists direct, deliver, and flexibly tailor the deployment of a range of treatment modalities for patients spanning psychotherapies, medications (and other neurobiological interventions), and professional communications (which facilitates social support management, legal, financial, occupational, and community assistance). Through these integrated modalities, patients can progress through recovery trajectories where they decrease or stop using different addictive drugs, experience major improvements in mental health, and achieve better social and occupational functioning. In response to the reality (see Chapter 4) that addiction and mental illness are complex and highly interactive brain diseases arising from many contributing factors, successful individualized plans of care designed by addiction psychiatrists often implement multiple therapeutic strategies and routinely seek out multiple treatment targets simultaneously. Much as prior text in this book has likened addiction to a cancer of motivation, diagnosis in addiction psychiatry prioritizes a clinical understanding of the extent of the impact and severity of the addiction and the co-occurring mental illness like staging of a cancer diagnosis. It then tries to leverage multiple concurrent and potentially intersecting strategies of care to "shrink the tumor of addiction (and comorbid mental illness)," much as oncologists use combination interventions to increase the chances of recovery and sustained remissions of neoplasms.

Treating Addiction and Dual Diagnosis as Chronic Diseases

As discussed in prior chapters, addiction is a *chronic* and *progressive* brain disease that can manifest with a waxing and waning course over weeks, months, years, and decades. Although typically seeded or launched in adolescence or young adulthood, it often evolves over years intertwined with undulating courses of mental illness symptoms. These illnesses

typically accumulate many physical (i.e., injuries and medical illness of body organs), social, financial, legal, and occupational damages that cannot be fixed overnight. As such, the treatment of addiction and dual-diagnosis disorders should be pursued for most patients as a long-term project. Although sudden and rapid gains in recovery can be achieved, recovery trajectories are often marked by phasic setbacks (e.g., relapses) or sudden breakthroughs, so that attention to both current and long-term patterns and arcs of recovery are of premium importance.

This "long game" (chronic disease) approach to addiction and dual-diagnosis treatment is an important perspective for both patients and addiction psychiatry professionals to grasp. It attends to the reality that the integrated brain diseases of addiction and mental illness have usually taken time to develop (months to years) and will often take time (months to years) to recover from. It also attends to a very common neuropsychiatric attribute that patients with severe addiction and dual diagnosis often have that clinicians need to be aware of and therapeutically address in order to generate momentum for the patient to achieve sustained patterns of recovery: the **foreshortened event horizon.** The foreshortened event horizon is a neuropsychiatric phenomenon where dual-diagnosis patients, especially those in active addiction, show an inability to plan for and organize behavior to achieve goals (or avoid negative outcomes) in the longer-term future. This nonspecific kind of "future blindness" is a manifestation of prefrontal cortical (and associated subcortical–limbic) dysfunction, which can have many etiological contributions, including histories of mild traumatic brain injury, different forms of underlying mental illness (ranging from primary psychotic and mood disorders to trauma-spectrum mental illness) and the brain toxicological effects of different addictive drugs. So, a patient's foreshortened event horizon can also be significantly exacerbated due to the acute and chronic effects of repeated cycles of drug and/or alcohol intoxication and withdrawal. A clear data-based illustration of this phenomenon is available (see Chapter 4, discussion on impulsivity and Petry, 1998). In this study, subjects with heroin addiction were compared with a control group of non-drug users in measures of cognition that reflect awareness and planning of future events and outcomes. This included an exercise where subjects were asked to finish an open-ended story about their personal futures. Remarkably, those in the control group created a story ending that

ranged about 4.7 years into the future, whereas those in the heroin-using group created a story that was *only 9 days* into the future. This foreshortened event horizon phenomenon has been linked with a range of various cognitive measures of **impulsivity**, most prominently including the exacerbation of **delayed discounting** where subjects consistently *and abnormally* prefer lesser, immediate rewards over greater, delayed rewards. This kind of impulsivity explains a great deal about the pathogenesis of addiction and its capacity to be acquired by patients, even when they know quite a bit about its potential long-term adverse consequences. Individuals with baseline impulsivity, characteristic of vulnerable adolescent and mental illness populations (see Chapter 4), can more easily develop addiction and fall into high-severity disease states. At the same time, long-term secondary consequences of current drug use, such as developing lung cancer or contracting HIV, are serious outcomes of addiction that will emerge probabilistically and relatively far into the future. A brain that is oscillating between phases of intoxication and withdrawal several times each day or week and is depleted of financial resources or healthy social connections often has very few cognitive resources to draw upon to comprehend, plan for, and act, to build a long-term future.

In part because of their foreshortened event horizons, patients with active substance use often *initially* engage unreliably with treatment due to a damaged motivational system that includes, among several issues, an impaired appraisal of the future. So, it is the job of the addiction psychiatry treatment team to expertly help patients acquire a better future orientation while helping them move through various cognitive, emotional, and motivational stages of recovery using all manner of psychotherapeutic, experiential, and medication-based tools as outlined in this chapter. Figure 5.1 shows a typical addiction recovery course as a person engages in long-term addiction psychiatry treatment. As the patient gains momentum into recovery, initial high-frequency cycles of intoxication and withdrawal (resulting in acute psychiatric/social/medical problems) gradually give way to longer drug-free phases and gaining of **recovery capital** (i.e., accumulation of social, occupational, or lifestyle elements and other advantages that support sustained sobriety). Throughout these recovery trajectories, the addiction psychiatry team maintains awareness that each acute gain or setback is merely a data point on a larger trajectory of recovery.

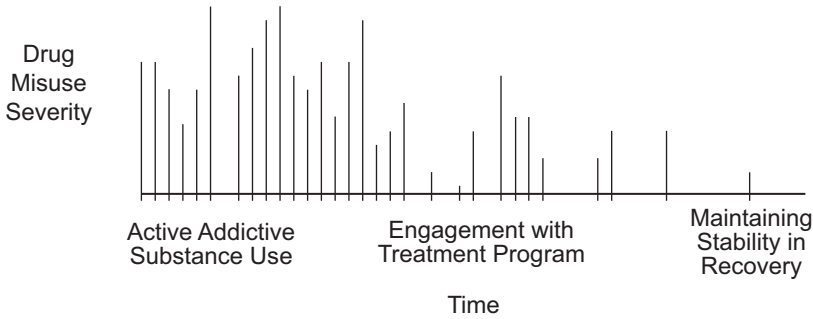

Figure 5.1 A typical addiction recovery course. In this conceptual example of a recovery pattern, each vertical line represents the amount of substance use the patient is doing in a single month. With recovery underway, relapses and binges can still occur at any stage, but they become less frequent and more limited in intensity and duration, with many patients eventually achieving total remission of substance use.

In keeping with the nature of addiction (and most forms of co-occurring mental illness) as chronic diseases, it is important to not only make a thorough diagnostic assessment at the initiation of care, but to continuously diagnose and monitor illness evolution and treatment outcomes longitudinally. Accordingly, sound addiction psychiatry care is an iterative process that shifts between repeated diagnostic assessments and treatment plan adjustments, where many mental health- and addiction-related variables are observed and tracked to inform a flexibly adjustable array of treatment strategies. As patients show sustained improvements, their recovery trajectories often asymptote at levels where treatment interventions can be pulled back or employed less frequently, and sometimes patients can be discharged from care in full remission on no medications (but always with a standing invitation to return to care if needed!). In this way, addiction is a chronic disease that shares attributes with many well-known chronic diseases of body organs, such as hypertension, type II diabetes, and asthma. Yet unlike many of these conditions, addiction can actually be cured, or at least permanently remitted, for the rest of the life of the patient. The progression and severity of mental illness, addiction, and these other medical conditions are affected by heritability and environmental experiences or exposures (Chapter 4). They all have

clear vulnerability factors that differ across individuals, and they all can lead to a host of other secondary or tertiary disease states. Successful treatment of chronic diseases requires repeated monitoring, for example via blood pressure, blood glucose, or pulse oxidation checks, or more specifically in the case of addiction, urine drug screening. As in the treatment of most chronic diseases, addiction recovery is fostered by combinations of both correct medication choices and adoption of healthier behaviors on the part of patients. Obviously, better compliance with treatment is associated with better outcomes across all these conditions. However, similar rates of poor compliance on the part of patients (<30% of patients show excellent treatment compliance) are observed across all these chronic medical conditions. Annual rates of major relapses (to significant illness exacerbation) ranging from 30% to 70% are also similar across all these chronic medical disorders including addiction.

Together, these similarities confirm our understanding of addiction as a common, chronic biomedical condition that, like these other general medical conditions, requires routine screening and preventive measures *especially* in general psychiatry settings (where addictions are present at extremely high rates). Once detected, addiction should be regarded as highly coincident and biologically contributory to mental illness (and vice versa) requiring expert attention and sustained healthcare practices based on provision of long-term therapeutic relationships. In addiction psychiatry, the interactive and iterative process of diagnostic monitoring and treatment plan modification serves both preventative and direct treatment purposes, frequently involving a focus on multiple concurrent addictions and mental illness syndromes within individual patients and across whole clinical populations.

Integrated Dual-Diagnosis Treatment versus Split-Care Models

Integrated dual-diagnosis treatment (IDDT) *refers to treatment that expertly recognizes and addresses diagnoses of mental health and addictions concurrently, and with equal prioritization*. Public health psychiatrists and researchers (Bob Drake at Dartmouth; Kenneth Minkoff at Harvard; Kim Mueser at Boston University; and many others) have been advocating for this merger of addiction and mental health care

since they introduced it in the 1980s. This merger carries significant advantages of therapeutic efficacy and efficiency. It avoids chaotic ***split-care*** models (also described as *siloed, segregated, or separated* care models), where dual-diagnosis patients can't get both mental health and addiction care at the same time and/or with the same treatment team or system.

Integrated dual-diagnosis treatment supports increased diagnostic accuracy, as patients are more likely to be diagnosed and treated for what they actually have, and not just what the name or mission of the treatment facility wants a patient's diagnoses to be. Unfortunately, in split-care models, the mental health clinic typically ignores or refers out for the addiction, whereas addiction clinics tend to ignore, undertreat, or refer out for mental health problem(s). However, as reviewed in prior chapters, the same brain regions, including within the limbic system (e.g., consisting of interconnected regions of the PFC, NAC, CA-PU, AMY, and HCF) are key brain sites where the neuropathologies of both mental illness and addiction occur and interact. A consequence of this reality is that it is not often easy or possible to separate one disease process from the other, either neurobiologically or clinically (especially for nonaddiction psychiatrists, or physicians working in siloed systems). Mental illness and addictions are intertwined to such an extent that an exacerbation or improvement in one will often affect the other. Environmental factors such as stability in occupational, financial, medical, relationship/social, and housing domains can similarly improve/worsen these illness categories. Because of the interactive biological and causal dynamics (and shared neurodevelopmental ingredients) of these illness categories (Chapter 4), patients with mental illness, addiction, or dual-diagnosis comorbidities also commonly experience evolution in their diagnostic "sets" over time. As mental illness biologically generates addiction vulnerability, people with mental illness often migrate into the "dual-diagnosis bucket." Similarly, people with severe addictions or multiple addictions (initially without substantial mental illness) also often migrate into the "dual-diagnosis bucket." Therefore, it should be understood that these are not static diagnostic populations. Instead, patients can readily flow between mental illness/addiction/dual-diagnosis categories over time (as if these diagnostic categories are like permeable membranes, and patients are like solutes that migrate across them). Given this spectrum of dynamic diagnostic

diversity and fluidity, the fully integrated dual-diagnosis treatment model – which rejects the idea that addiction and mental health issues should be handled by different (unconnected) specialty clinics and clinical teams – is best equipped to diagnose and treat the entire spectrum of behavioral health patients.

The draw backs of siloed/split care models extend also into problems with treatment communications, efficacy, and coherency. Due to the protected nature of healthcare records, especially those involving a mental illness or addiction diagnosis, split care can make vital communications between segregated professionals extremely difficult, often resulting in conflicted and disorganized treatment strategies. Split care models also tend to reinforce a culture among providers that they should only manage and be responsible for "their piece" (either the mental illness or addiction part) of the patient's behavioral health illness and prognosis (despite the fact that the patient's mental health and addictions illnesses are biologically and clinically interrelated). This situation can result in providers not taking full responsibility for patient care, or not adequately addressing poor outcomes, because poor treatment responses in dual-diagnosis patients can always be blamed on the "other" component of the illness (that the siloed clinic believes it is not responsible for) or the other outside doctor or clinic that is taking care of the other component of illness. The psychiatrist who ignores or refuses to ask about or test for substance use can often fail to recognize why some of their patients are **refractory** (i.e., unresponsive) to mental health treatment. In many cases, this scenario may lead to ineffective or inappropriate treatment plans involving medications. For example, merely increasing the dose of an antipsychotic or prescribing multiple antipsychotics will likely not provide adequate medication coverage to overpower psychosis that is being exacerbated by heavy cannabis and/or methamphetamine use in a patient with schizophrenia or bipolar disorder. The same is true for cases of treatment-refractory depression, in which patients have substance use disorders that are clinically ignored. In many patients with serious addictions, where high rates of personality disorders are fairly common, split treatment models can also facilitate pathological splitting and manipulation, involving multiple healthcare providers. This kind of splitting can be a symptom of a patient's mental illness (e.g., especially borderline personality disorder) or the addiction itself, where patients can pathologically convey inconsistent information

to different clinical teams, attempting to manipulate one team into being in conflict with another. Not uncommonly, this kind of splitting can result in extremely dangerous prescribing patterns where different types of controlled substances are being prescribed to one patient simultaneously from different clinics and providers that are not in communication. In this kind of split-care scenario, which is unfortunately all too common, medications can be iatrogenically harmful, treatment plans chaotic, and prescribers operate more as product delivery "middlemen" of addictive pharmaceuticals, rather than as clinical experts dedicated to the long-term recovery of patients.

As suggested in Figure 5.2, split care for addiction and mental health (in contrast to IDDT) also creates a number of logistical inefficiencies and wastage of services. Ironically, while both addiction and mental health

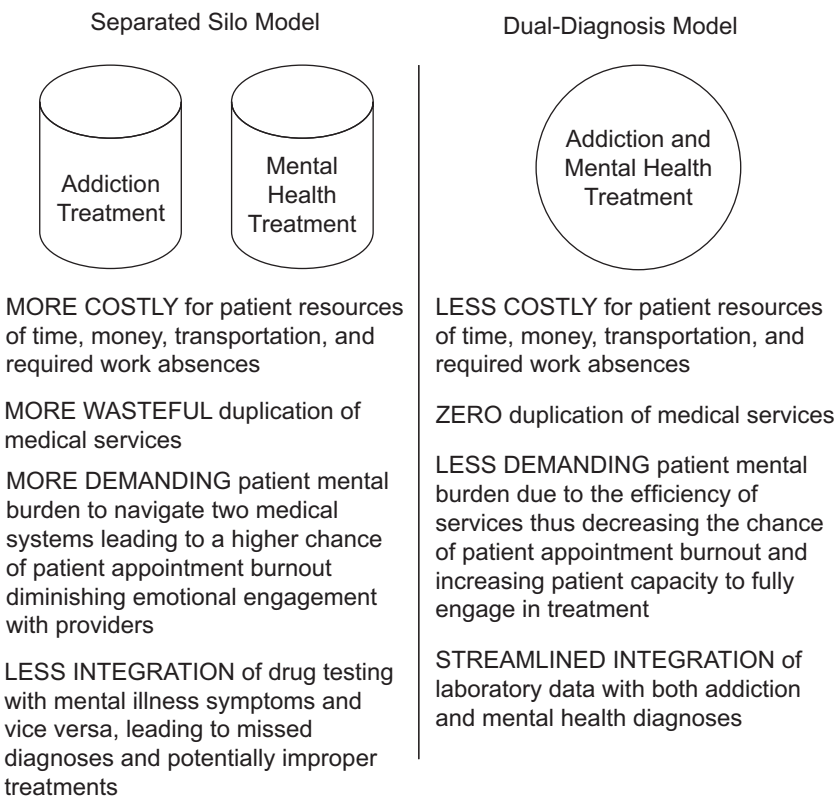

Figure 5.2 Spit-care versus integrated dual-diagnosis treatment (IDDT).

providers remain in short supply, segregated care models actually force patients with mental illness and addiction into having two different physicians (or prescribers, in the case of nurse practitioners) and, often, two different sets of therapists. This can wastefully duplicate work from medical providers while requiring more patient time, additional days off work, higher transportation burden, and greater financial costs to the patient (or insurance for supporting treatment at two different venues). In contrast, IDDT strives for efficiency, coherency, comprehensive efficacy (outcomes pertaining to both addiction and mental illness treatment are prioritized), and centralization of services. The IDDT approach can thus provide superior efficacy and cost-effectiveness in supporting a patient's financial status, and occupational autonomy, while reinforcing strong therapeutic alliances with members of a single treatment team (who are all working on the same treatment plan) as an essential ingredient to long-term recovery.

The 2×4 Model: A Neuroscience-Based Union of Addiction Psychiatry and Integrated Dual-Diagnosis Treatment

Addiction psychiatrists are uniquely formally trained and board-certified to treat the full spectrum of mental illness, addictions, and their many comorbid combinations. This expertise optimally positions them to treat the full spectrum of behavioral health patients, regardless of how a given patient's dual-diagnosis illness comorbidity combination may change over time with either illness worsening or recovery. As such, addiction psychiatrists are optimally trained and suited to lead and provide IDDT as well as being the most expertly versatile in the management of patients who happen to have mental illness–only or addiction-only diagnoses. The first *neuroscience-based framework* for addiction psychiatry clinical care, training and research, the **2×4 model**, was introduced as a textbook for addiction psychiatry fellowship training in 2018. The 2×4 model aims to modernize and empower the integrated dual-diagnosis movement by (1) providing a basic neuroscience rational and foundation for the full integration of mental health and addiction services, training, and research, and (2) explicitly merging the IDDT movement with the profession of addiction psychiatry.

Some of the key neuroscience that provides motivation and justification for the merger of mental health and addiction services and

expertise is described in Chapter 4. This body of research can be described as an example of **translational neuroscience**, insofar as the basic neuroscience that explains dual-diagnosis phenomena has implications for how we can optimize clinical training and service delivery. So, given that the brain biology, causative ingredients, and neurodevelopmental mechanisms that generate mental illness and addiction vulnerability are so tightly interlinked, bidirectionally interactive, and commonly comorbid, it does not make sense (and is inconsistent with the evidence base) to treat these disorders in highly fragmented, chaotic, split-care formats. On the other hand, when directing and practicing in an IDDT program, the addiction psychiatrist and their clinical team are expertly capable and maximally equipped for treating the entire spectrum of mental illness, addiction, and dual-diagnosis comorbidities. Meanwhile, patients and families can be assured that the teams of physicians, nurses, therapists, case workers, peer supports specialists, and so on who work together in a 2×4 model addiction psychiatry clinic are optimally trained and prepared to manage a patient's recovery, regardless of how their behavioral health comorbidities may evolve over time, and without having to disrupt vital therapeutic bonds (which siloed care models constantly do). In this "one team/under one roof/for as long as it takes to get the patient better" approach, the 2×4 model formalizes the IDDT approach and puts its implementation in the hands of doctors who are uniquely and explicitly trained and board-certified to do so. Much as the neuroscience of dual diagnosis is an **integrative neuroscience** (i.e., it integrates/connects the neuroscience of addiction and mental illness), it also calls for the integration of addiction and mental health clinical training and care services.

The 2×4 model blueprint for the fully integrated, team-based, addiction psychiatry clinic gets its name from how it is conceptually designed as a 2×4 component grid (Figure 5.3). The "2" components, on the vertical "Illness" class dimension, emphasize equal prioritization and expertise focusing on both (1) mental illness and (2) addictions. The "4" components, on the horizontal "Treatment" dimension, emphasize the key tools and techniques that must be available and flexibly deployed to conduct (1) diagnostics, (2) psychotherapies (and other **experiential treatments**), (3) medications (and other **biomechanical interventions** like neurostimulation), and (4) communications in the treatment of the

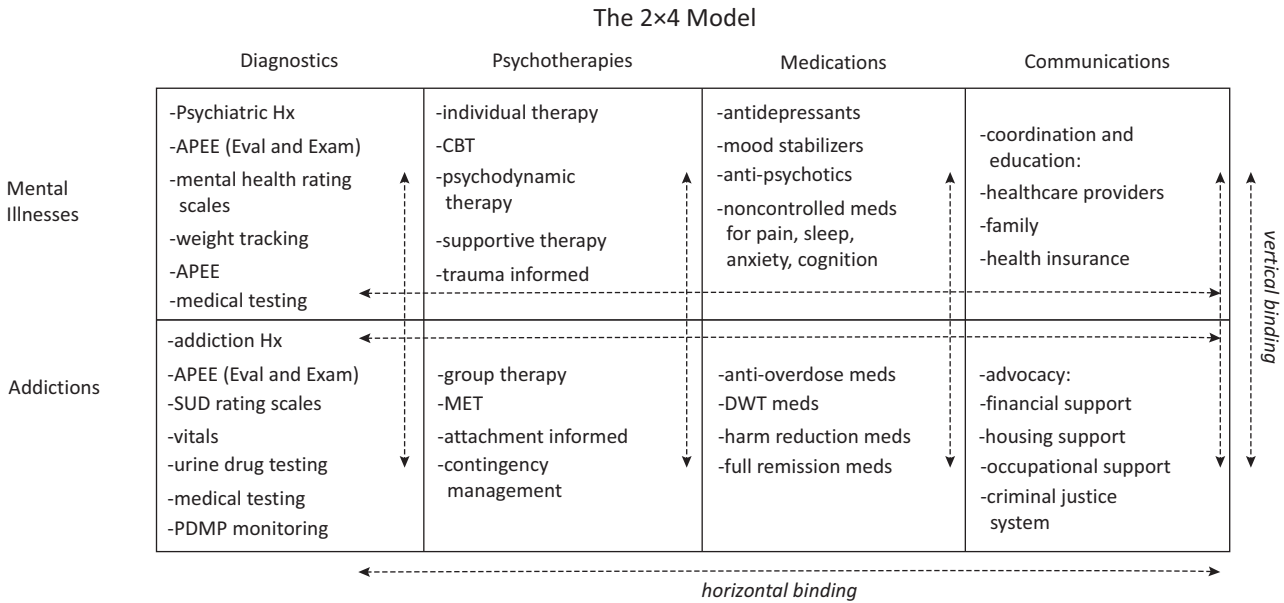

Figure 5.3 The 2×4 model: integration of dual-diagnosis neuroscience, IDDT, and addiction psychiatry. The 2×4 model addiction psychiatry clinic is equipped with addiction psychiatrists, nurses, and therapists that can provide fully integrated addiction and mental health care: A "one team under one roof" model that can treat the entire spectrum of mental illnesses, addictions, and their comorbidities. Vertical binding ensures that the team is equipped with tools and techniques for integrating diagnostic and treatment components for both (or either) mental illness or addiction. Horizontal binding ensures integration and coherency between the diagnostic and outcome tracking work and the various treatment plan components (psychotherapies, medications, and communications).

patient. **Vertical binding in the 2×4 model** emphasizes the need to ensure that all modalities of evidence-based diagnostic, psychotherapeutic, medication and communication efforts are sensitive to and efficacious for both mental illness and addiction disorders *to whatever extent these two main illness classes may be present in a given patient*. Thus, the addiction psychiatrists and other allied professionals in the 2×4 model team are expected to be fully IDDT capable. **Horizontal binding in the 2×4 model** emphasizes the importance of diagnostics, psychotherapeutics, medication management and professional communications as all being mutually interdependent, informative, and coherently integrated endeavors of the clinic. Diagnostic work is repeatedly conducted for any given patient to measure outcomes and update treatment plans that may involve psychotherapies and medications. In turn, psychotherapies can help with diagnostics while informing medication choices; medication choices can alter diagnoses (via improvement in specific mental illness or addiction components) while influencing behavior and success in psychotherapies. Finally, communications sent out by the addiction psychiatrist and or other team members to outside stakeholders (primary care, insurance companies, criminal justice system officials, child protective services, housing or disability support agencies, lawyers) are aimed at optimizing the patient's environmental conditions, supports, and recovery capital. Well-placed communications directed outside the clinic protect access to and synergize with the care and recovery that is happening within the addiction psychiatry clinic. Such communications should be comprehensively informed by what is happening with the patient diagnostically, psychotherapeutically, and medication-wise. By being comprised of an interdisciplinary team of addiction psychiatrists, nurses, and therapists working and communicating together under the same roof, according to a unified and coherent treatment plan, the 2×4 model design facilitates both vertical and horizontal binding and coherency across all the major components of IDDT. This coherency, represented by communications delivered to partners and stakeholders outside the addiction psychiatric clinic, can have a powerful impact in accelerating and maintaining recovery in combination with psychotherapies and medications. Extensions of the core 2×4 model team can include general psychiatrists, child psychiatrists, nurse practitioners, pharmacists (in the case of clinic-embedded pharmacies), primary care

providers, legal advisers, and peer recovery specialists all operating as a team and fundamental unit of a broader public health system.

Diagnostics and Outcome Tracking in Addiction Psychiatry

There are three main pillars of diagnostic and outcome tracking in addiction psychiatry:

(1) Addiction psychiatry evaluation and exam (APEE).
(2) Drug testing and prescription drug monitoring program data (PDMP) inquiry.
(3) Clinical engagement and collateral input tracking.

Implementation of these three diagnostic approaches should be repeated throughout the course of the patient's care, spanning all phases of treatment (see **DWT, HR, and FR strategies** below). All three of these diagnostic modalities are integrated with and inform the delivery of both psychotherapeutic and medication-based modalities of treatment.

The Addiction Psychiatry Evaluation and Exam

In addiction psychiatry, the physician is evaluating and tracking illness signs and symptoms across *all* the mental health and addiction comorbidities a patient may present with over a long-term trajectory of recovery (weeks/months/years). The initial APEE (i.e., the clinical interview performed by the addiction psychiatrist) is the most important, first-tier element of the diagnostic work up (see Table 5.1). It occurs as an initial evaluation (taking about an hour to perform) and is followed up by repeated, shorter versions (focused on evolving histories of present illness (HPI), reviews of systems (ROS), and exams) in 15–30 min sequential appointments over the longitudinal course of care. These follow-up appointments occur at frequencies determined by the physician and patient, ranging from more than once a week to every 6 months, depending on the complexity and severity of the illness comorbidities and the need for monitoring (e.g., if controlled substance medications are being prescribed).

Table 5.1 Outline of the initial addiction psychiatric evaluation and examination

ID	Identity; patient's age, gender identity, occupation
CC	Chief complaint; quote from patient stating major problem(s) and/or reason for seeking care
HPI	History of present illness narrative; describes the patient's recent illness course as an interwoven syndrome involving both addictive drug use and mental illness symptoms as interactive disease processes. Or, when one illness class (addiction versus mental illness) is predominant, the narrative reflects that. The story should also detail the pathway of recent events that led them to this evaluation
ROS	Review of symptoms: Listing of nonspecific mental illness, neurological, or medical symptoms not already covered or central to the HPI; "neurovegetative" symptoms (pertaining to sleep, appetite, sexual function, energy level); pain levels and sources; current medication side effects
Past SUD HX	Investigate substance use history as a separate strand: Cover timelines and treatments for the big seven (nicotine, alcohol, cocaine, amphetamines, opioids, benzoids, cannabinoids) and special addictions, overdoses
Past MI Hx	Investigate mental illness history as a separate strand: Cover timelines of symptoms and treatments for mood-anxiety, trauma and psychotic spectrum disorders, hospitalizations, suicidal thinking and attempts, self-injurious behavior, traumatic experiences
Social Hx	Where the patient grew up, siblings, educational level, marriages, children, divorce, gender identity, sexual orientation, occupations, legal history, where living, income
Medical Hx	Active medical problems, medical meds, past and upcoming surgery
Exam	Appearance, behavior/gait, speech, mood, affect, thought process, thought content, estimated intelligence, cognition, judgment/insight
Assess/ plan	Diagnoses statement; plan of psychotherapies, meds and communications

The APEE builds on methods and elements typically covered in the general psychiatric evaluation and mental status examination. However, it puts a greater premium on achieving the best balance of attention to diagnostic content pertaining to *both substance use disorders and mental illness*. A *heavy focus on social history* is also important for uncovering information on how the patient's mental illness(s) and addiction(s) may have interactively developed, and what secondary damages these illnesses had for the patient. In general, the well-done addiction psychiatry evaluation is more complex and requires more skill on the part of the doctor than a general psychiatry exam usually entails (which is one reason fellowship training in addiction psychiatry is recommended!). The added challenge of the addiction psychiatry interview comes from needing to cover more ground in terms of history gathering, while also working to establish a high level of trust, rapport, and credibility from the perspective of the patient. In the APEE, the addiction psychiatrist is managing three key tasks to conduct the best possible interview:

(1) *Achieving efficiency, flexibility and focus of clinical data capture*: More clinical ground (pertaining to both addiction(s) and mental illness(s)) must be covered per session; the interviewer must develop a reliable sense of knowing when to focus on big-picture versus fine-grained information pertaining to a specific diagnosis and knowing which diagnoses in the patient's comorbidity set needs greater attention.

(2) *Establishing "buy in" and the beginning of a therapeutic bond*: A successful therapeutic alliance in addiction psychiatry is a two-way street. Addiction psychiatrists are constantly aware of this reality and the impact of their interactions with patients. Patients are evaluating and communicating with the physician, just as the physician is evaluating and communicating with the patient. It goes without saying that if the patient feels like the physician is treating them in a condescending, judgmental, dismissive, or uncompassionate way, or is otherwise treating the patient like a number, as a part on an assembly line, or as an object of an economic exchange, it is far less likely that the patient will come back to see the doctor or listen to what they recommend in the treatment plan. Concurrent documentation should be avoided as much as possible during the evaluation, while maintaining good eye contact and active engagement with the patient. Although these principles certainly apply to general psychiatric interviewing, applying them in addiction psychiatry is a greater challenge due to two major factors

that are particular to patients with addiction. First, they are particularly sensitive to being dehumanized, stigmatized, judged, and punished for having addiction as a consequence of their past experiences. Often, a natural reaction most people have to such treatment is to run from it. Second, by the very nature of addiction disease, they are to some extent *pathologically allied with the addiction* and compulsively motivated to continue to use whatever drug(s) they are addicted to. This drug motivation is in essence not only competing with the patient's natural healthy motivation to survive (nearly all chronic addictions are lethal if not treated), but it is competing with or attempting to work against the therapeutic alliance and relationship that the addiction psychiatrist is attempting to establish. Thus, both the difficulty and therapeutic benefits of effectively establishing trust and therapeutic bonding are particularly strong in addiction psychiatry interviewing.

(3) *Invoking a therapeutic impact*: As an extension of points 1 and 2, the addiction psychiatrist leverages the clinical interview not only to collect diagnostic information but to generate a therapeutic impact. This requires skills that encompass the ability to maintain a *psychotherapeutic stance* throughout the interview, as well as having mastery of psychopharmacology (pertaining to the treatment of both mental illness and addictions), while being able to rapidly design and modify short- and long-term treatment plans that integrate multiple therapeutic tools from these domains. Finally, these plans must be communicated effectively with patients, even as they have differential capacities to absorb and act on this information.

Table 5.2 lists some of the key elements of the APEE, highlighting how it differs from or adds to what is performed in the classic general psychiatry evaluation (the reader should consult a general psychiatry textbook for a more detailed description of a general psychiatric evaluation and mental status exam, e.g., Kaplan & Sadock's *Synopsis of Psychiatry*). The APEE can be supplemented with a range of accessory diagnostic tools like rating scales for opioid (**clinical opioid withdrawal scale, COWS**) or alcohol withdrawal (**clinical institute withdrawal assessment alcohol scale, CIWA**), the **adverse childhood experience – questionnaire (ACE-Q)**, and objective tests of cognition (**Montreal cognitive assessment, MOCA (mocacognition.com)** or **Folstein mini-mental state examination**), or remote wearable telemetry technologies (e.g., that can measure sleep or physical activity).

Table 5.2 Addiction psychiatry evaluation and examination key elements

Evaluation	Examination
Drug use timelines: For all major drug classes (*nicotine, alcohol, cocaine, amphetamines, opioids, benzoids, cannabinoids*) determine timelines of use (age of onset, frequency/extent of use at peak and recently, date and time of last use).	**Appearance:** Physical signs of drug use (e.g., cigarette stains on fingers, vape/cigarettes on their person, smelling of substances like alcohol, tobacco, marijuana, needle marks, state of dentition, body weight and shape).
Consequences of drug use: Check for *medical* (e.g., infections, organ damage), *psychiatric* (e.g., history of overdose or withdrawal, drug-induced psychosis/mood), *legal* (history of arrest or incarcerations related to drug use), *financial* (e.g., homelessness, money spent on drugs), *educational* (e.g., couldn't finish college), *occupational* (e.g., inability to hold a job or preference for jobs that provide drug access), *social* (e.g., divorce, estranged from family).	**Behavior/gait:** Signs consistent with intoxication or withdrawal of a substance. Drug-seeking behavior (pushing or attempting to convince/manipulate the prescriber with an indication for stimulants, benzoids, opioids). **Speech:** Signs of intoxication. **Mood:** Expressions of anxiety in withdrawal. **Affect:** Irritability/impatience in intoxication, withdrawal, or drug seeking. **Thought process:** Signs of intoxication.
History of prescribed controlled substances: (benzodiazepines, opioids, stimulants).	**Thought content:** Craving severity; thoughts supporting drug seeking; drug preferences or ranking of perceived difficulty in stopping; level of motivation for treatment (stages of change); psychosis, suicidality, or risk of violence linked with recent use.

History of periods of sustained sobriety: How this was achieved.

Past addiction treatment history: (inpatient/outpatient/meds).

Social barriers to care: (e.g., instability in transportation, housing, income).

Review of use in family and social network: Determine those in active use versus sobriety.

Triggers and rationales for drug use: What makes them crave? Does patient believe they are "self-medicating"?

Cognition: Deficits in short- and long-term memory, language, and calculation skills as possible damage from substance use

Insight: To what extent are they aware of their addiction and the actions it causes.

Judgment: Current levels of impulsivity, and ability to inhibit drug seeking and use; propensity for risk-taking behavior.

Drug Testing and Prescription Drug Monitoring Program Inquiry

Understanding what psychoactive drugs the patient may be using, and assessing their exposure to, or compliance on, controlled (prescribed) treatment meds, are mandatory elements of the diagnostic workup and outcome tracking in addiction psychiatry. Indeed, drug use monitoring typically done with **urine drug screening (UDS)** and **PDMP** inquiry are as important and fundamental to the practice of addiction psychiatry as the stethoscope and EEG are to cardiology! Mastering the use, interpretation, and medical decision-making based on drug testing and PDMP inquiry takes clinical experience and training (e.g., as gained in an addiction psychiatry fellowship). The optimization and integration of these diagnostic tools is actually quite complex and could be the subject of a separate textbook. So, for the purpose of this introductory textbook, we will only briefly outline their uses here.

In drug testing, there are four key parameters of interest that have to be balanced and are hard to optimize all at the same time: (1) speed of return of results; (2) accuracy of results (sensitivity and specificity); (3) scope of results (how many drugs tested for); and (4) cost. Rapid test kits (enzyme assays in a test cup) that give a positive or negative result (but no quantitative levels) in a few minutes after sample collection are great in terms of speed and cost ($5–$15), but they are not good for accuracy or scope. Rapid tests can lack **sensitivity** (failing to detect a drug when it is there, producing a **false negative**) **or specificity** (misidentifying a drug as being there, or misidentifying one drug for another, producing a **false positive**), whereas "send out" testing, in which samples are tested in an outside lab for drug levels using various forms of chromatography, are very accurate (and indeed, are considered gold standard) and quantitative (give a number that expresses drug concentration in the fluid). However, these high-fidelity tests take longer (days to weeks) to return a result and cost more ($20–$300 plus). Generally, drug testing should be done routinely, randomly, and quantitatively (e.g., with chromatography methods), with rapid testing supplementing the send outs on occasions when immediate results are needed.

The scope of drug testing should include assays for all the major legal and illicit drug groups (nicotine, alcohol, cocaine, marijuana/THC, heroin) and controlled prescription drugs that can cause iatrogenic

harm (amphetamines, benzoids, opioids). It should also include a capacity to differentiate and quantify drugs from within each of the main stimulant, opioid, benzoid, and cannabinoid families, as facilitated by testing for drug metabolites. Assays for metabolites can be crucial in understanding the *time course* of recent use. In the case of alcohol, real-time alcohol (ethanol) levels can be assessed by breathalyzer testing or testing of samples from serum or urine. In contrast, the recent cumulative pattern and volume of ethanol consumption can also be inferred, even after all ethanol has been metabolized, by detection of **ethyl glucuronide (ETG)** in urine (e.g., assessing alcohol use over the last week) or **carbohydrate-deficient transferrin (CDT)** in serum (assessing alcohol use over the last month). A capacity to evaluate levels, metabolites, or cofactors of prescribed drugs used to treat opioid addiction (methadone and 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP); buprenorphine and norbuprenorphine with naloxone) can also be key to assessing medication compliance.

A final parameter to consider in the use and interpretation of drug testing is the consideration of what body compartments samples are drawn from (e.g., hair, saliva, breath, blood, urine, and so on) and how they are collected (observed, unobserved). Each of these approaches have their pros and cons, for speed, accuracy, scope, and cost. Also, the modality and manner of collection (observed versus unobserved) has significant psychological and interpretative implications for the patient and the treatment team. In general, UDS testing should be done in the addiction psychiatry clinic by treatment team members, and not relegated to a different location or outside agency.

The main goal of drug testing is to document longitudinal *patterns* of active drug use (or recovery) as a key objective measure for tracking illness severity and treatment outcomes. Single test results are not as important or informative for clinical decision-making as multiple test results collected over time. Drug testing results in the addiction psychiatry clinic should never be used to punish patients or be handed over to third parties that may use the information to harm or punish the patient or remove them from treatment. The exception to this guideline comes into play in the case of subpoenas, court-room testimony, or court-ordered disclosure of medical records. In addiction psychiatry, drug testing should be used strictly for medical-diagnostic purposes as part of a constructive effort to build trust in the therapeutic relationship, to

educate and advise patients, and to inform treatment planning and medical decision-making.

Serial UDS results are used together with repeated PDMP data inquiries to get an evolving picture of what addictive/controlled drugs the patient is using or being exposed to (e.g., iatrogenically) over time. PDMPs are state government–sponsored online databases that track the prescribing and filling of controlled substance prescriptions (i.e., for DEA-scheduled psychoactive drugs that have adverse intoxicating, addictive, and/or overdose potential). All US states maintain PDMP databases and require all outpatient commercial pharmacies to report all their controlled prescribed dispensations within a week to the PDMP database. All licensed prescribers can check PDMP data on their patients at any time, providing them with a quite detailed summary of the types, quantities, prescribing instructions, dates of writing, dispensations, and/or sale of all controlled medications to the patient over a selected period of time. The PDMP database also includes a complete accounting of prescribers' and pharmacies' identities and addresses, and how prescriptions were paid for. Generally, PDMP data should be examined at every appointment for every patient in the addiction psychiatry practice, with findings briefly documented in the chart, especially when significant, clinically relevant changes in controlled prescribing to the patient are identified.

Clinical Engagement and Collateral Input Tracking

The third tier of diagnostic assessment and outcome tracking comes from assessing (a) levels of clinical engagement (with physician, nursing, and psychotherapy appointments), and (b) input from collateral sources of information (e.g., from collaborating therapists inside the clinic, or from other physicians, family members, or criminal justice professionals outside the clinic). Clinical engagement and collateral data can provide important indicators of the patient's motivation and commitment to recovery and assessment of ongoing behaviors and symptom levels observed outside the clinic by friends, family members, or other members of the patient's recovery support system.

Together, these three tiers of diagnostic assessment – (1) the APEE, (2) drug testing and PDMP, and (3) clinical engagement/collateral input tracking – should be integrated (and documented regularly in clinical charting) to form a powerful data stream of subjective and objective

information that allows the addiction psychiatry team to wholistically track the patient's evolving diagnosis and recovery trajectory. In the 2×4 model format of integrated addiction psychiatry practice (Figure 5.3), these three tiers of assessment are used to track the broad spectrum of mental illness and addiction syndrome features, and treatment outcomes that make up the temporal patterns of recovery trajectories unique to each patient. The addiction psychiatrist monitors and integrates these diagnostic data streams to navigate treatment planning and drive medical decision-making, much as an airplane pilot integrates information about fuel, weather, speed, altitude, position, and heading to navigate and pilot the flight course of their aircraft.

Treatment Tools and Phases in Addiction Psychiatry

The diagnostic work and treatment of patients with addiction and dual diagnosis begins with the very first encounter between the patient and the addiction psychiatry team leading up to the initial encounter with the addiction psychiatrist. In general, there are three main categories or phases of addiction treatment that can happen in various ways (e.g., partially, simultaneously, sequentially, or repeatedly) for a given patient, depending on their degrees and types of mental illness and addictions comorbidities, and, of course, their level of engagement. To use the analogy of addiction disease being like a monster running wild in the patient's "house" (causing all kinds of damage to their mind, motivation, relationships, occupation, health, and so on), we can summarize the three treatment phases of recovery as follows:

(1) **Detoxification and withdrawal treatment: *Apprehending the monster***
(hours to weeks): The patient starts cutting back or completely stops using a given drug(s). Psychotherapies and medications are deployed to treat and support passage through substance withdrawal.

(2) **Harm reduction: *Containing and controlling the monster***
(weeks to years): Often with sustained psychotherapeutic support, the patient has stopped a much more dangerous form of addictive drug use while being treated with a therapeutic medication that is of the same

pharmacology or class as the addictive drug target (e.g., the therapeutic drug could also be capable of causing intoxication and/or addiction if used incorrectly). However, the medication or other method of HR when deployed under appropriate, controlled, clinical supervision offers excellent safety and capacity to control or limit the damage being created by the addictive drug(s). This modality of care when done pharmacologically is also often termed "**maintenance**," "**substitution**," or "**replacement**" therapy (not preferred terms).

(3) Full remission (FR): *Eliminating the monster*
(weeks to years): With the support of psychotherapies and medications that do not replicate the addictive pharmacology of the target addiction (yet while pharmacologically reducing craving and relapses) the patient can more readily and sustainably stop using the addictive target drug, achieving a long-standing patterns of total drug abstinence. Chronic craving and relapses are extinguished to minimal clinical relevance, providing the patient with a full divorce from the drug. This modality is also often termed **"abstinence"** (not a preferred term) **or "cessation" therapy**, allowing long-term disease remissions that can be as strong as or represent a "cure."

Given that patients with addiction and dual diagnosis often have multiple addictions and mental illness diagnoses at the same time, it should be understood that patients could be in different phases of treatment at the same time with respect to the different drugs they are trying to recover from. For example, a patient on an inpatient unit getting DWT (receiving benzodiazepines for alcohol detoxification) could also be using nicotine gum on the unit (instead of smoking) as an HR therapy. In addition, each of these phases of treatment (depending on the target drug in question) can have different effects on the underlying mental illness(es) that may be present (e.g., opioid withdrawal can greatly exacerbate depression and anxiety; alcohol withdrawal can exacerbate psychosis; amphetamine cessation can lead to improvements in anxiety and psychosis but cause depression). The addiction psychiatrist maintains an ongoing focus on the underlying mental illness during any and all of these phases, and an awareness of and readiness to therapeutically intervene as needed.

In the next section on psychotherapies, we will temporarily hold off on discussing more details about DWT, HR, and FR phases of treatment as they correspond more directly with what is happening in the medication strategy for the patient. However, the reader should understand that psychotherapies are also important to deploy both within and across

these three phases of treatment and can be tailored to both the phase of treatment and the patient's *motivational stages of change*, introduced below.

Psychotherapies and Experiential Treatments in Addiction Psychiatry

Psychotherapy is a key modality of psychiatric treatment in which the supportive professional relationship, the content of conversation (or other forms of creative expression such as art or music), and the discovery of new insights about the patient's thinking, emotions, motivations, and behavior can enhance the speed and solidity of recovery. Psychotherapy should be done by professionals trained in the discipline. Good therapists for mental illness and addiction need training through a mix of didactic instruction, independent reading, and clinical supervision in which a mentor is working with the therapist-in-training on specific clinical cases. Although people may be innately talented at delivering psychotherapy, it still takes training and mentoring to become proficient as a therapist. Excellent therapists are good at (a) enjoying the work with a range of simple to complex problems; (b) setting up safe, trusting, nonjudgmental, and confidential bonds with patients; and (c) are able to maintain good boundaries (e.g., never, ever getting into an intimate personal, sexual, or otherwise exploitive relationship with patients).

Psychiatrists are the only physicians of any medical specialty that are required to be formally trained in psychotherapy, although different residency programs (and the motivation, interest, and talent of the psychiatry resident) can have a substantial impact on the scope and depth of this training. Master's-level mental health or addiction counselors, social workers, psychologists, and nurses can also be psychotherapeutically trained. Ideally, these professionals work in collaboration with the psychiatrist, who is typically making diagnoses and prescribing medications. The psychiatrist should also be engaging the patient using a **psychotherapeutic stance** (i.e., being aware of the psychodynamics of their interactions with the patient and acting within a psychotherapeutic framework). **Psychodynamics** refers to the cognitive, emotional, motivational, social, communicative, and behavioral events that arise between the therapist and the patient in the psychotherapy. Among these are the **transference**, which refers to the patterns of interactions and reactions patients have with their therapist, as

a reflection of their past relationships. **Defense mechanisms** (e.g., projection, projective identification, splitting, denial, introjection, minimization, reaction formation, and so on) are elements of a suite of possible social-behavioral and cognitive patterns that patients demonstrate within the psychotherapy, which may reflect differential forms of psychopathology and/or traumatic experiences from past relationships. In addiction psychiatry, patients often use defense mechanisms as ways to manage or hide conflicted or uncomfortable feelings, cognitions, motivations, including those that may be supporting drug-seeking.

Of course, every psychotherapy (and indeed every relationship) is a "two-way street." So, the therapist also has their own patterns of interactions and reactions to their patients called the **countertransference**, influenced in part by *their* past relationships. In the practice of psychotherapy, the therapist is always maintaining an awareness of both the transference and the countertransference. They are focused on both the patient and their own behaviors and interactions with the patient. This "fourth wall" skill of observing what is happening in the therapeutic relationship, including monitoring of how they themselves are thinking, feeling, and acting in the relationship, is an important way for therapists to pick up on diagnostic clues about the patient, and for choosing, delivering, and monitoring the impact of therapeutic interventions. Through the monitoring of their countertransference and awareness of the emerging psychodynamics in the therapy, the psychiatrist/psychotherapist also obtains greater endurance, boundary awareness, and overall enjoyment in the work, regardless of how sick patients may be. Thus, the psychodynamic stance is useful not only for diagnostic and therapeutic purposes but for helping the clinician easily tolerate and contain (not personalize or adversely mirror or react to) the pathological behaviors that the patient may be enacting. It allows psychiatrists to maintain intellectual engagement and gratification in the work with the patient even when patients could be showing disease-related behaviors that are off-putting, disappointing, or frustrating, especially early on in treatment, when relapses are frequent.

Going beyond using a psychotherapeutic stance, psychiatrists can also practice a full-on psychotherapy as integrated with medication management. There are many schools, theories, and forms of psychotherapy that inform its delivery, quality, focus, intensity, duration, and goals. However, the most effective approaches overlap considerably (or share common ingredients and skill sets on the part of

the therapist) in terms of how they provide efficacy. To a significant extent, the efficacy of psychotherapy is dependent on the talent and training of the therapist, as well as the quality of the person-to-person "chemistry" that underpins the strength of the therapeutic bond between patient and therapist. This skill level consideration is more of a factor for a 1:1 psychotherapy as compared to a group therapy format. But either way, the skills and potential impact of the therapist are important and yet can vary considerably from person to person.

Regardless of the specific modality, the psychotherapeutic treatment of addiction and mental illness (and their comorbid presentations) generally involves at least one of three or more mechanisms that drive efficacy. *First, there is the power of the* ***therapeutic relationship*** *or bond (****attachment****) itself.* Having an intelligent, sober, reliable, well trained, and compassionate professional to talk to, who is familiar with the way the mind works when it is suffering with mental illness and/or addiction, is a way for patients to know *and feel* that someone is on their side and that they are not alone in whatever battles they may be fighting. Humans (whether healthy, mentally ill, and/or addicted) are built to interact socially, and are generally empowered emotionally, motivationally, and cognitively when they are working toward the same goals in groups of two or more (realize that an individual "1:1" psychotherapy is a special case of a group psychotherapy, albeit one that has a total membership of two). In the therapeutic relationship, a kind of positive, supportive peer pressure is in play, with an attachment formed that is not coercive or adversely manipulative while focused on benefiting the well-being of the patient. For some patients, their therapist and/or psychiatrist may be the only people they regularly contact who are sober, are well educated, and are not out to use the patient for some deleterious purpose or transaction. The transformative power of the therapeutic relationship, especially in addiction treatment is particularly important for helping patients displace their addiction with healthy motivations and attachments. Addiction itself is a disease of brain mechanisms that subserve motivation and attachment, and as patients become addicted over time, they tend to select social contacts and relationships that involve other people who are using and supplying addictive drugs. Therefore, the formation of a healthy attachment through the psychotherapeutic alliance is a way for patients to work against this disease-driven tendency, and to get positive reinforcement and guidance as they pursue recovery.

A second mechanism of efficacy involves discovering and learning new insights about oneself and the brain disease(s) patients are grappling with, and developing new ***mental tools*** *(cognitions and behavioral habits) that can work as weapons against the disease.* Again, the therapist is professionally trained, and sober, and so is equipped with a more objective ("clear-eyed") and professionally educated view of the patient's behavior and cognitions that may be supporting the addiction/mental illness beneath the patient's own awareness. Moreover, they are trained to convey these insights and tools of recovery in ways that the patient can best absorb, tolerate, or enact, all while being attuned to the patient's stage of recovery and capacity for change.

A third mechanism of efficacy in the therapeutic alliance happens as the therapist works as guide, advocate, and coordinator. When the therapist is not the psychiatrist on the case, they can certainly assist with medication management that the physician is doing by relaying diagnostic information to the doctor that may be coming up in the therapy. The therapist may also be recommending/guiding **experiential modalities of recovery**, for example, changes in lifestyle or living conditions that can enhance recovery, such as help with disability income or housing. In equipping patients with mental tools and experiential modalities of recovery, the therapist/psychiatrist helps the patient build **recovery capital** (again, referring to the accumulation of habits, opportunities, resources, and social connections that both support sobriety and allow sobriety to be meaningful and gratifying for the recovered patient).

In whatever ways psychotherapy may be working to facilitate recovery, it is important to understand that these mechanisms work because they have a neurobiological impact of some kind. A commonly held myth among many people (even some healthcare professionals) is that psychotherapy is not a biologically active treatment, whereas medications are. This is not the case. The formation of a healthy, supportive attachment, and therapeutic alliance is a neurobiological process that involves neuroplastic changes in specific regions of brain anatomy that are involved with and impacted by mental illness and addiction disease. Learning and practicing new insights, tools, and habits (like any form of learning) involves neuroplastic change in specific regions of brain anatomy. Being guided into new experiences or lifestyle approaches or contexts (e.g., increasing exercise or moving into better living conditions) as facilitated by the therapist, are contextual changes that alter the brain's

"information diet" and its internally generated neurohormonal milieu. Of course, these environmental influences will impact the patient's responses to medications, at the very least by changing the patient's capacity to be compliant with medication treatments. So, both psychotherapies (i.e., therapeutic social experiences) and medications are neurobiologically active interventions that have the ability to either temporarily or permanently alter the brain. Under many (but not all) circumstances, most patients can benefit optimally from having some mixture of psychotherapeutic and medication management approaches (hence why the 2×4 model requires the availability of psychotherapy and medication approaches and capacity for their integration as delivered by one treatment team).

Types, Formats, and Techniques of Psychotherapies in Addiction Psychiatry

It is beyond the scope of this book to detail all the major forms of psychotherapies, and so we will cover only select ones that are among the most commonly delivered and best supported by evidence in the addiction psychiatry setting. Certainly, it is the case that skilled therapists (and well-equipped addiction psychiatry clinics) offer an eclectic array of psychotherapy forms and techniques that should be individualized to some extent, depending on the diagnostic needs and capabilities of the patient. A big-picture way to classify psychotherapies is as individual (1:1) versus group psychotherapies (involving a therapist and two or more patients, and typically up to a 1:16 ratio). Both these modalities should be available to addiction psychiatry patients (as a requirement for the 2×4 model approach) as they have different sets of strengths and drawbacks for different diagnoses and patients.

Individual psychotherapies carry the advantages of providing greater focus, intensity, flexibility of scheduling, active patient participation, and airing and protection of personal confidential information. Individual therapy is also generally more responsive and flexible to individual diagnostic needs and the capabilities of the patient (as a participant or receiver of psychotherapy). The downsides of individual psychotherapies are that they are much more costly to deliver and do require more skill on the part of the therapist (at least in terms of knowing how to use and mix different approaches), with a bit more luck thrown in relating to nature

and strength of the attachment (i.e., the "chemistry" of the therapeutic bond). **Group psychotherapies** rely on and engender the power of not just the therapist but the group of peers in the therapy to create therapeutic change for as many patient members as possible. Professional group therapies in addiction psychiatry treatment often run on manualized schedules or proscribed curriculums, which makes them inherently less flexible than individual psychotherapies. At the same time, this structural overlay can be particularly useful in groups given that they are comprised of different individual personalities and patients who may be quite diverse diagnostically. Indeed, the wild card element and double-edged sword of group therapy is that its efficacy (or lack thereof) for any one patient can depend on the nature and quality of the participation and behavior of other patients in the group. The challenge for the skilled group therapist is to keep the group on task (whether the group is manualized or not) in facilitating recovery for everyone in the appropriate balance. This is done by influencing the pace and distribution of group member participation while managing the focus of the group's attention. At the same time, the group leader strives to maintain and leverage a culture of safety and mutual support in the group. The group therapist must also be aware of not just the content of group discourse (sometimes referred to as **group content**) but the phenomenon of **group dynamics** (sometimes referred to as group process). Group dynamics (very much akin to politics) refers to how members work together, or in competition, or in conflict; how members assume or assign each other certain roles (including leadership and followership); how individual members' psychodynamics mix and interact on a group level to create an emergent group process. The group process can take on its own identity, attitude, and vibe, existing almost like its own life entity or collective personality (sometimes referred to as the "life of the group"). By observing what is happening in group dynamics, the skilled professional group leader can offer insights or interpretations about the group that can move the group (and individuals in it forward) much as the therapist in the individual setting can provide observations and insights to the individual patient.

Stages of Change

The **transtheoretical model**, commonly referred to as the **stages of change (SOC)**, was developed by Prochaska and DiClemente in the early 1980s. It is a clinical framework that can be used to observe and constructively intervene on the progress patients make in creating significant, enduring behavioral changes necessary for reducing a health threat or improving their lives. Essentially, the SOC, described in detail in Table 5.3, couches the process by which motivation to make

Table 5.3 Stages of change

Stage of change	Definition	Example
Precontemplation	Individual does not recognize they have an addiction problem and does not feel they have a need for change.	Despite being intoxicated at work, patient does not think it has affected their work quality (has never been reprimanded), so assumes it must not be an issue. Concerned comments from coworkers or family are ignored.
Contemplation	Individual recognizes addiction is posing a problem and begins to think about pros/cons of potential solutions.	Patient receives official feedback from work about drinking behaviors and realizes their job could be in jeopardy. Now open to receiving pamphlets about different treatments for addiction, although makes no plans about what they would do.
Preparation	Individual begins planning how they will attempt to address/reduce/treat their addiction behaviors.	Patient begins to think about their triggers for alcohol use and wonders if they can stop alcohol completely or if they could use in moderation. Seriously compares treatment programs or modalities and picks the one(s) that seems best.

Table 5.3 (cont.)

Stage of change	Definition	Example
Action	Individual enacts prepared steps of plan.	Patient attends appointments where they actively work with doctor and therapist to design and implement treatment plans. Adheres to appointments and psychotherapeutic and medication modalities of treatment; able to have honest conversations about successes and setbacks without abandoning treatment or judging self.
Maintenance and Relapse Prevention	Individual creates and sustains a modified motivational-behavioral repertoire and recovery capital in which active addiction has no representation; maintains better mental health and life success in sobriety with strong resistance to relapse.	Patent forms new motivations and habits to decrease/cease alcohol use; surrounds themself with supportive friends/family; uses and enjoys new powers of sobriety; minimizes or is immune to triggers. Life stressors are no longer major triggers; mental health proactively maintained.

a change is generated (**precontemplation**/**contemplation**), how that motivation is translated into behavior (**preparation**/**action**), and how the behavior is sustained to create enduring change (**maintenance**/**resistance to relapse**). As the reader will readily appreciate, the SOC has applicability to a broad array of behavioral challenges (e.g., weight loss, ending a destructive relationship). SOC is also relevant to helping

patients manage healthy adaptations to major life transitions (e.g., as in grief responses), in which parallels have been noted with Kubler-Ross' stages of grief (depression/anger/denial/bargaining/acceptance; see Chambers and Wallingford, 2017). However, treating and recovering from addiction has been the most direct and widely adopted application of the SOC.

One of the most powerful aspects of the SOC as it is applied in addiction psychiatry is that it serves as both a diagnostic-observational framework and as a target point or orientator for therapeutic interventions. Knowing how prepared and behaviorally committed a patient may be to their recovery on the SOC gives the clinician an understanding of the patient's insight and level of healthy motivation that they need to push against the pathological motivation that represents the addiction disease. Through **motivational interviewing (MI)** (a style of psychotherapy described below) the clinician gains a fairly accurate appraisal of where the patient is on their SOC progression with respect to a given addiction (note that this appraisal can be documented in the APEE described previously in the Thought Content section of the Mental Status Exam). In the application of **motivational enhancement therapy (MET)**, which uses the MI approach, the clinician is leveraging the therapeutic dialogue to facilitate and boost the patient's motivation and progression across the SOC into the action and maintenance phases of recovery.

Motivational Interviewing, Motivational Enhancement Therapy, and Cognitive Behavioral Therapy

In **MI**, the clinician adopts a nonjudgmental/nonpunitive stance and, in many ways, a nondirective approach. So, rather than telling the patient what to do, the therapist focuses as much as possible on discussion that allows the patient to discover, develop, and act on their own healthy motivation and best course of action. The MI approach elicits a more open and honest discussion about the patient's insights, cognitions, and motivations surrounding their addiction, while also fostering the therapeutic alliance between the clinician and patient against the addiction. Because society has so ingrained attitudes of stigma, judgment, and punishment against addiction (and the patients afflicted with it), by framing the disease as a religious sin or crime, it actually takes training and practical experience for addiction psychiatrists and allied

clinicians to shed the social–emotional and language-based habits of stigmatization, blame, and judgment (which is necessary for getting skilled at MI). But once proficiency in MI is reached, the clinician can achieve a relatively accurate view on the patient's illness (*relatively* unobstructed by the patient's minimization and denialism), while gaining major influence on supporting the patient's own motivation to enact recovery. In **MET**, the clinician assesses where the patient is on their SOC with respect to a given addiction and is working to facilitate (or *enhance*) the patient's healthy *motivation* so that they are more likely to translate that motivation into action that will put the addiction further into a state of remission. In MET, done with the MI approach, the therapist is engaging in conversation with the patient that explores their cognitions and motivations for change (**"change talk"**). This is also done with the airing of cognitions and motivations that support the status quo of continuation of the drug use (or the behavioral addiction; **"resistance talk"**). As the clinician and patient discuss these kinds of opposing motivational forces harbored in the patient's brain (and literally represented in some way within the neural networks of the patient's nucleus accumbens), there are many opportunities for the clinician to support and reinforce change talk and undermine or question resistance talk. Eventually, the change talk (as a reflection of brain-based motivational processing) can occupy a larger space in the context of the therapy, and thus be more likely to ignite or sustain behavioral action toward recovery. Notably, one of the most common resistance talk themes that patients will describe is the framing of their drug use as a form of "self-medication"; for example, rather than the use being understood as detrimental, it is perceived or justified by the patient (or rather, the cognitions generated by the addiction disease) as providing some kind of mental or physical health benefit (see Chapter 2 **myth-busters**). Once an addiction is diagnosed, it is important for the clinician to beware of the dangers and inaccuracies (of objective evidence) of this kind of drug-use justification, and not fall into the trap of being convinced by the patient (or rather the patient's addiction) that this resistance talk has merit enough to abandon treatment and recovery from the addiction.

In the adaptation of **cognitive behavioral therapy (CBT)** to addiction psychiatry, the clinician is working to give the patient more insightful perspectives on and abilities to change their cognitions, motivations,

emotions, and behaviors that surround drug-use triggers, urges, drug-seeking, and drug relapses. A good portion of this work is the identification and dichotomization of **drug-use triggers** into two classes: (1) those that are unavoidable and need to be confronted and (2) those that are avoidable. Drug triggers can be any kind of stimuli, experience, context, person, place, emotion, time of day, thought process, and so on that can initiate intense craving or trains of behaviors that lead to relapse. When relapses do occur (and they often do during the course of recovery), CBT focuses retroactively on an analysis of the cognitive and behavioral chain of events that led to the relapse. This analysis can help the patient better anticipate, confront, or avoid particular triggers or steps in the chain that led to the relapse. Again, the MI approach is critical to the success of CBT for addiction, because it facilitates more honest airing and communication of all the actual events, mental phenomena, and behaviors that were part of the relapse episode. Obviously, patients who are afraid they will be judged and punished for relapsing are more likely to hide the relapse from the clinician altogether, in which case the relapse cannot be addressed therapeutically and the patient becomes more engaged in a deceptive alliance with the addiction to conceal it from the clinician.

Mixing Styles and Tools in Individual and Group Psychotherapies

Individual psychotherapies for addiction and dual-diagnosis disorders are best carried out with an eclectic, flexible approach where clinicians use an MI approach with a mix of MET, CBT, and psychodynamic stances and techniques (Table 5.4).

Group therapies for addiction and dual-diagnosis disorders can also utilize techniques that are done in 1:1 therapies (MI, MET, CBT, psychodynamics), but typically provide greater nonindividual-specific education about the diseases (of mental illness or addiction) or their treatments. They also provide guided leveraging of peer support and collective wisdom of the group members toward the benefit of individual group members. Structured (manualized) or free-form curricula in professional group therapies for addiction often borrow elements and perspectives used in **12-step (Alcoholics Anonymous (AA)/Narcotics Anonymous(NA))** programs, which are not professional *(i.e., members*

Table 5.4 Basic psychotherapies for addiction and dual diagnosis

Type of psychotherapy	Goal of therapy
Motivational enhancement therapy	Therapy that uses a nonjudgmental-collaborative style of interviewing (motivational interviewing) that strives to minimize ambivalence for and support motivation for change (or recovery). Addiction causes pathological reluctance to change and alliance with addiction, despite harmful consequences from continued substance use. The therapist helps to guide the patient toward change but prompts the patient to come up with the solutions to increase autonomy and responsibility. Asks the question: "What are the pros and cons of staying in addiction versus recovering?"
Cognitive behavioral therapy	Goal-oriented problem-solving approach used to change or acquire new behavioral patterns. Examines how an individual's thoughts, feelings, and behaviors affect one another. Can often involve homework assignments of tracking progress between sessions with a focus on cravings and trigger management. Asks the question: "What practical solutions can be used to reduce a problem or trigger?"
Psychodynamic psychotherapy	Insight-driven therapy that seeks to uncover the semi-conscious or unconscious motivations associated with a person's cognitions, emotions, or actions. Utilizes a strong therapeutic relationship developed over time to examine transference and pathological defenses. Can be useful for exploring trauma and patterns in relationships (familial, romantic, friend) to see how they have contributed to addiction risk. Asks the question: "What experiences and relationships caused a person to have psychiatric or addiction disease and how can they grow beyond them?"

and leaders in the group are not formally trained or paid to do the work of the group) but can offer excellent support and wisdom for people in recovery. Professional group therapies for addiction often incorporate three major themes distilled and adapted from 12-step programming, which also roughly corresponds to the SOC:

(1) Recognizing there is a brain disease that impairs free will, requiring external help/treatment
(SOC: precontemplation to contemplation)

(2) Acknowledging and acting on the need to repair damage caused by the disease
(SOC: preparation/action)

(3) Role modeling and supporting others seeking addiction recovery and mental health
(SOC: maintenance/relapse prevention)

Typically, however, in distinction to AA or NA, professionalized adaptations of 12-step themes focus more on understanding addiction as a disease rather than as spiritual or character failure, while framing the "required external help" as coming from evidence-based treatments, well-trained professionals, and support from recovering peers. Also, in addiction psychiatry (in distinction to 12-steps groups) there is full acknowledgment, acceptance, accommodation, and treatment of co-occurring mental disorders, and utilization of medication treatments for both mental illness and addiction. In the 2×4 model addiction psychiatry clinic this integration includes medications with provisions for individual and group psychotherapies.

Aside from 12-step–based approaches, there are many other techniques and forms of group therapy that have been developed for patients with addiction and dual-diagnosis disorders. Two notable examples include Seeking Safety and Circle of Security ©. **Seeking Safety** was developed specifically as an integrated group therapy for the comorbidity of PTSD and addiction common to Veteran's Affairs (VA) settings. This approach facilitates the development of CBT-based coping skills against both PTSD and SUDs, with attention to breaking patients away from pathological cognitions or dysfunctional coping in which the PTSD could be driving the ongoing substance use, or the substance use is keeping the patient stuck in, or vulnerable to, worsening PTSD. Because

trauma-spectrum illness and symptomatology and past traumatic events are so common among addicted and dual-diagnosis patients, even among those without full PTSD diagnoses, seeking safety has broad applicability to treating a wide range of dual-diagnosis patients. **Circle of Security** © is a form of professionally directed group (or even individual) psychotherapy in which pregnant women or women with young children are the focus of treatment. In this approach, the overarching goal is to support the formation of better attachment (between moms and their perinatal or young children) and enhancing parenting skills in young parents who may have various comorbidities of mental illness and addiction. This therapy may have special utility for patients with their own histories of being raised by parents who could not provide strong or healthy attachments and parenting. Because of its target population, theoretical orientation based in attachment theory, and being amenable to deployment in addiction psychiatry clinics with a perinatal focus, Circle of Security © has significant potential for not only helping parents and children simultaneously, but for interdicting the transgenerational transmission of the nongenetic (environmental causal determinants) of addiction and mental illness.

Experiential Treatments

Experiential treatments for addiction and dual diagnosis are directed sensory experiences or changes in behavioral sets, lifestyle patterns, and/or **reinforcement schedules** (engagement in natural experiences that motivate and gratify as alternatives to drug use) that support treatment and recovery. Experiential treatments can take many forms and can be supported by or integrated with individual or group psychotherapies. Three widely applied forms of experiential treatments, each with various degrees of neuroscientific support, include:

(1) ***Regular cardiovascular exercise***: Supports well-regulated eating and sleep cycles, is mood-protective, offers stress resilience and anti-craving. Biologically supports neuroplasticity, neurogenesis (see sections at end of this chapter), and endogenous neurotransmission underpinning natural euphoria and subjective states of well-being.

(2) ***Contingency management***: Patients receive rewards (small monetary or other benefits) or chances for rewards contingent on evidence for

successes in obtaining sobriety and/or showing significant recovery. Contingency management is a method to support natural motivation to not use substances (i.e., a form of motivational enhancement) that is reinforced by the delivery of concrete material reinforcers for recovery-oriented behavior. For example, a clinic could respond to an appropriate urine drug test result by delivering the patient a raffle ticket or monetary reward. This evidence-based modality has various forms, for example, employers requiring professionals to be in recovery before returning to high-paying jobs, or, conversely, not pairing participation in treatment with high-cost medical billing (experienced as financial punishment for being in recovery).

(3) ***Engagement in the arts*** (music/visual art/theater performance): Supports creative expression and social communication and connection apart from drug use. Mood-protective; offers stress resilience and natural pleasure. Can be directly combined with psychotherapy (e.g., via music therapy or art therapy). Biologically supports neuroplasticity and cognition (note: high-powered musical and performance arts careers can, however, increase susceptibility to addictions (e.g., via overexposure to party culture, fame, or isolation), or attract creative talents that may be associated with mental illness and addiction risk factors).

It is important to mention that engagement in various other experiential treatments including cognitive exercises (e.g., game playing) and sensory experiences (meditation, acupuncture, message, spiritual activities) can also produce therapeutic benefits for patients in recovery in terms of building stress resilience and quality of life that imparts significant resistance to relapse. Understanding how these experiences can biologically impact the brain and enhance recovery from mental illness and addiction are interesting areas of research.

Medications and Neural Modulation for Addiction and Dual-Diagnosis Disorders

The pharmacological treatment of the various phases and stages of addiction should be integrated with psychotherapeutic interventions as much as possible (e.g., in the 2×4 model, the same addiction psychiatry team delivers both treatment forms in a coherent–collaborative way). Moreover, the medication management of co-occurring mental illness

should also be conducted in a coherent, evidence-based approach that is also integrated with addiction care. Ideally, and in the 2×4 model approach, medication management for mental illness and addiction(s) should be done *by one physician* to reduce the risk of adverse, chaotic, and contradictory **polypharmacy prescribing** (i.e., too many meds, high risk of multiple controlled drugs prescribed). In contrast, **split-care** prescribing comprised of multiple prescribers (who are typically not in communication with each other) delivering multiple psychotropic drugs to the same patient are unnecessarily costly, ineffective, and potentially harmful.

It is beyond the scope of this book to review the entire compendium of psychiatric medications used in the treatment of mental illness and substance use disorders. The reader should consult large-volume psychopharmacology textbooks for a more comprehensive and in-depth survey of the many medications that are used in addictionology and mental health care. Here, we will describe the main concepts and common examples of addiction treatment medications across DWT, HR, and FR stages of recovery with the understanding that this review focuses on the addiction side of addiction psychiatry pharmacology.

Detoxification and Withdrawal Treatments: Apprehending the Monster

As previously suggested, DWT is often the first step in initiating addiction treatment as a way of *apprehending the addiction monster*. However, DWT is not always a needed or necessary first step in recovery, depending on the type and pharmacology of the drug the patient is trying to stop using. Although all drugs and their intoxication states (especially with chronic heavy use) will lead to withdrawal syndromes of some kind, fortunately only a few of these withdrawal states are typically extremely uncomfortable or medically dangerous. Essentially, there are three major classes of drugs that patients should be closely monitored and treated for in the DWT phase of care when patients are starting to sharply decrease or cease substance use. These classes of drugs and the basic risk levels of their withdrawal syndromes are listed in Table 5.5.

DWT helps patients achieve *short-term* substance abstinence in a way that minimizes the suffering and medical danger of withdrawal syndromes. Recall, per Chapter 2, that drug withdrawal is actually

Table 5.5 Major drug withdrawal syndromes needing medical attention

Drug class	Subjective distress	Medical risk	Duration	Core treatment
Opioids	High	Moderate/ low	5–14 days	Opioid taper or clonidine + adjuncts
Benzoids	Moderate/ high	Moderate	5–21 days	Benzodiazepine taper/antiseizure meds
Alcohol	Moderate	Moderate/ high	5–14 days	Benzodiazepine taper/antiseizure meds

a manifestation of the homeostatic neurobiological adaptive changes that the brain makes in the chronic presence of a substance to allow the brain to function as normally as possible when the substance is on board. Withdrawal syndromes emerge when the brain's homeostatic adaptations to the drug are unmasked by the sudden absence of the drug. The more heavily and chronically a person uses a drug, the more profound and sustained these adaptations are, leading to a more severe and prolonged withdrawal syndrome when the drug use is sharply reduced or stopped. Notably, the 1–3-week duration of the major withdrawal syndromes listed in Table 5.5 roughly reflects the time it takes for the brain to biologically readapt to the sustained *absence* of the drug. Notice also that the three major classes of drug withdrawal syndromes (which often require professional medical attention, in contrast to the milder withdrawal states produced from stimulants, nicotine, cannabinoids, or hallucinogens) all share characteristics of being central nervous system (CNS) depressants. This reflects the fact that the withdrawal state to these drugs is essentially a hyperstimulated, hyperexcitatory, hypersympathetic discharge state of the brain, as if the brain were overheating, approaching what happens when a person is suffering from **status epilepticus** (seizures that don't stop). Indeed, seizure thresholds are certainly lowered for an individual in all three of these withdrawal states, particularly in benzoid and alcohol withdrawal syndromes. Accordingly, in all three syndromes, the brain's hyperactive state literally reflects a situation where there is too much

release of the brain's basic excitatory neurotransmitter glutamate, which can be both **neurotoxic** (i.e., can harm or kill neurons) and lethal (by producing a neuropsychiatric storm with cardiovascular arrhythmias and collapse) in the case of **delirium tremens** with alcohol withdrawal. Hence the treatment of these withdrawal syndromes generally involves the application of various medications that help blunt central and peripheral nervous system overactivity.

Withdrawal syndromes from other addictive substances that are not CNS depressants (cannabis, cocaine, amphetamines/methamphetamines, nicotine, and so on) are of course physiologically real but typically correspond more with CNS depressive states. Although these states can certainly produce depressive symptoms, irritability, and transient mild cognitive symptoms (indistinguishable from ADHD), they are typically not very severe or medically risky. So, their treatment does not need to be as medically aggressive or requiring of inpatient care.

Regardless of which withdrawal syndrome is being treated (and remember, patients might be suffering though very complex withdrawal syndromes in response to multiple substances), *treating withdrawal itself does not treat the underlying addiction*. Rather, the provision of DWT (as a way of apprehending the addiction monster) is the first and sometimes medically necessary step to what comes next: containing or eliminating the monster. Unfortunately, many different types of settings that treat drug withdrawal, such as emergency rooms, inpatient psychiatry units, short-term detox centers, or rehabs, often provide services in a way that is disconnected from longitudinal outpatient addiction psychiatry care. This lack of integration presents a common barrier against appropriate transitions in addiction care, often resulting in patients who go through multiple cycles of withdrawal and relapse. To prevent this sort of breakdown in the continuity of care (and to make up for the lack of reliable, quality inpatient services for addictions and dual-diagnosis disorders), the addiction psychiatry clinic can provide outpatient DWT for a subset of appropriately selected patients. In general, inpatient DWT is a bigger commitment of time for the patient and is far more costly than outpatient care. But it does produce higher success rates toward the goal of completing a passage through a withdrawal syndrome. It is also safer, cutting down on the risk of patients relapsing, diverting, or misusing controlled drugs in failed attempts to treat withdrawal. Perhaps the most important value of the inpatient setting is that patients are given

medications (and can get aggressive dosing) under medical supervision, while it is virtually guaranteed that they will not be relapsing or substituting inappropriately with other drugs that could greatly complicate the clinical picture. Inpatient DWT is more the approach of choice for patients who have significant medical and psychiatric comorbidities, have polydrug withdrawal syndromes, have previously failed to succeed in outpatient detox, have no safe or stable place to live while undergoing detox, or who have histories of significantly unstable withdrawal episodes (e.g., becoming suicidal or psychotic, having seizures, organ failure, and so on). Table 5.6 provides an overview of commonly used DWT medications that can be deployed in various combinations and dose regimens in the outpatient or inpatient setting for opioid, benzoid (including benzodiazepines, atypical benzodiazepines, barbiturates), and alcohol withdrawal.

Harm Reduction Treatments: Containing and Controlling the Monster

There are many forms of treatment in medicine that can be understood as harm reduction. To the extent that a disease is causing harm and its treatment (or recovery from it) requires a long-term effort, or cannot necessarily be expected to be decisive, harm reduction is treatment that allows the patient to live better with the disease while preventing it from getting worse or having secondary medical, psychiatric, or life-threatening consequences. From this perspective, a cast on a broken arm can be viewed as a type of harm reduction, as is insulin for diabetes.

In addiction psychiatry a range of treatment measures fall under the category of harm reduction. **Clean needle-sharing programs** are one of the more traditional examples. In clean-needle programs, patients with iv drug addiction can get clean needles legally. Like all legitimate, evidence-based HR strategies (which is all we are considering in this book), clean-needle programs have been proven to be effective in preventing infection (and infection spread) as a consequence of iv drug use. Contrary to the assertion of skeptics, clean-needle programs do not promote or increase iv drug use, and in fact, if they are affiliated with formal addiction treatment programs, they can facilitate the recovery of patients out of iv drug use. Similarly, the delivery of **naloxone to prevent a lethal opioid overdose** is a major way to prevent sudden death due to opioid addiction.

Table 5.6 DWT medications

Medication	Targeted withdrawal symptom	Mechanism	Notable side effects
Clonidine (Catapres) Lofexidine (Lucemyra)	Opioid withdrawal: anxiety, sweating, tremor, agitation	Alpha-2-adrenoreceptor agonist	Somnolence, hypotension, rebound hypertension, fatigue, headache
Loperamide (Imodium)	Opioid withdrawal: diarrhea	Binds to opiate receptor in intestinal wall	QTc prolongation
Prochlorperazine (Compazine)	Opioid withdrawal: nausea, vomiting	Blocks dopamine receptors in brain and GI tract	Anticholinergic effects
Hydroxyzine (Vistaril)	Opioid withdrawal: anxiety, insomnia	H1 receptor antagonist	Anticholinergic effects, drowsiness
Ibuprofen (Advil)	Opioid withdrawal: aches and pains	NSAID: inhibits COX-1 and COX-2	Heartburn, dizziness, ulcers
Benzodiazepines: chlordiazepoxide (Librium), diazepam (Valium), clonazepam (Klonopin), lorazepam (Ativan), etc.	Alcohol/benzodiazepine withdrawal: taper over 1–2 weeks; for uncomplicated benzoid dependence, taper over weeks to months	Potentiates inhibitory GABA transmission	Respiratory depression, CNS depression, paradoxical aggression, fall risk, potential for seizures in withdrawal
Gabapentin (Neurontin)	Alcohol/benzodiazepine/opioid withdrawal: general symptoms of agitation, seizure risk	GABA analog	Respiratory depression, CNS depression

With either clean-needle programs or naloxone, we are reducing the medical and lethal harms of the addiction without necessarily directly treating or curing the addiction itself. Still, these techniques keep the patient healthy enough and alive long enough for more decisive, long-term treatments to have an opportunity to come into play.

Harm Reduction with Substitution/Replacement/ Maintenance Therapies

There are essentially three major forms of long-term HR pharmacotherapies for addiction that are overwhelmingly supported by the evidence base. Two of these are methadone and buprenorphine for opioid addiction; the other is nicotine substitution for nicotine addiction. These treatments are often termed as substitution, replacement or maintenance therapies because they essentially deliver the drug (or a *version* of the drug class) the patient is addicted to in a maintained (delivered chronically) form and format that is far safer – medically and psychiatrically – than what the uncontrolled drug use in the context of the active addiction involves. In all three of these treatments, there is a special pharmacology and/or form of delivery of the drug that allows it to be therapeutic rather than contributory to the disease. Moreover, with methadone and buprenorphine treatment, there is the manner of delivery, monitoring, and professional care that goes along with the medication that further enhances the medication efficacy and safety.

Opioid replacement therapy with either methadone or buprenorphine has been shown by an overwhelming body of evidence accumulating over decades to improve clinical outcomes and prolong the lives of people with opioid addiction in just about every way outcomes have been examined. This includes decreased risk of mortality from overdose, decreased rates of medical and psychiatric hospitalizations and consequences, decreased criminal–legal involvement, and increased occupational functioning. For the indication of opioid addiction, both drugs, which are very long-acting (with a 24-hour or longer **half-life** – requiring a day or more for half the dose entering the body to be metabolized), should be prescribed once daily and taken at a consistent rate (e.g., not as a "PRN" where patients take them intermittently "as needed"). The exact recommended duration and dosing levels of replacement treatment with methadone or buprenorphine should be individualized. For some patients, the best plan is a life-long plan (like

insulin for type 1 diabetes), whereas for others it is possible to taper the replacement therapy out in weeks, months, or years, as part of a plan that aims to achieve full illness remission from opioid addiction.

Methadone is a *long-acting, full mu opioid receptor agonist*. It is usually considered clinically effective at 60–120 mg per day and has an average maintenance dose of about 80 mg daily. Peak plasma drug levels occur about 4 hours after oral dosing, and it has a half-life averaging about 22 hours (but can vary from this average for many individuals). Methadone can carry a significant risk of overdose if not properly monitored, if the dose is raised too quickly, or if it is mixed with other substances or medications that cause respiratory depression, such as other opioids, benzodiazepines, or alcohol. Methadone also carries a risk of **QTC prolongation** (prolonging the electrical conduction wave in the heart as measured by EKG), which can lead to fatal arrhythmias – especially if combined with other QTC-prolonging medications like tricyclic antidepressants or certain antipsychotics/SSRIs. When prescribed for opioid addiction, methadone treatment is highly regulated and controlled by federal and state laws. These laws require that methadone be dispensed in a liquid oral form daily, delivered to patients directly. Thus, there is no intermediary pharmacy involved, and patients must take their daily medication in the clinic under some supervision, in order to avoid diversion and secondary distribution of the medication away from the clinic. Notably, although this format of care can be challenging for many patients, it is far safer (and less liable to diversion) than the legal way methadone is prescribed for chronic pain indications, in which prescribers give patents 30–90-day runs of methadone pills to take in a totally unsupervised way. Individuals in treatment at methadone clinics can eventually earn take-home doses for many days if they show stability in their drug testing and assessments. Methadone treatment carries two major advantages over buprenorphine treatment, although for most patients, buprenorphine is probably the best approach for people needing opioid replacement therapy. First, methadone at higher doses, as a full mu agonist, can reach greater potency levels than buprenorphine. So, certain patients may find that methadone does a better job of eliminating urges and craving. Second, some patients really benefit from the rules, structure, and consistent behavioral patterns that get set up by the frequent in-person visits they must make several times a week to the methadone clinic to receive the medication.

Buprenorphine is a *high-affinity, high-potency, long-acting, partial mu opioid receptor agonist*, meaning that it binds to the opioid receptor very tightly, and with strong potency at lower doses, while causing less peak activation compared to full opioid agonists like methadone or prescription pain pills. So, although at low doses (2–8 mg) the drug is quite potent, increasing the dose from 8 mg to 16 mg provides nonlinear increases in efficacy (diminishing returns), so that between 16 mg and 24 mg a day the efficacy of buprenorphine asymptotes. Therefore, it is very hard to overdose on the drug because even with high doses ($\gg$24 mg), where the drug is essentially saturating all the opioid receptors, there is not full efficacy at any of the receptors. Because the drug is so sticky at the receptors it also prevents most other opioids that may be in the patient's system from binding. With this special action, buprenorphine can actually produce paradoxical opioid withdrawal in people who are recently using other high-potency opioids. At the same time, consistent use of buprenorphine can block other opioids (relapses) from getting on the receptor and driving more addictive behaviors and even overdose. When formulated with the naloxone (the mu opioid receptor blocker) co-ingredient, buprenorphine is packaged in a way that somewhat helps prevent inappropriate buprenorphine use (e.g., by snorting or iv use), because the naloxone delivered with the drug via these alternative (nonsublingual) routes will be relatively more bioavailable and blunt inappropriately rapid/strong buprenorphine action. The naloxone co-ingredient probably also helps protect patients from lethal overdoses from other opioid relapses. Figure 5.4 shows the relative activities of general high-potency full agonist opioids (methadone, heroin, oxycodone) versus buprenorphine versus naloxone at the opioid receptor. This graph succinctly summarizes much of the comparative pharmacology of these drugs that determines their clinical utility.

Daily maintenance of buprenorphine can vary widely across individuals ranging from 4 to 16 mg a day. Pregnant women may benefit from doses as high as 24 mg a day (toward the end of pregnancy) and are usually prescribed buprenorphine without naloxone to prevent teratogenic risks of naloxone for the fetus. In most patients, peak levels are often achieved about 1–2 hours after dosing and the half-life is about 32 hours. Buprenorphine has very poor bioavailability when swallowed so it must be dosed sublingually. Patients are instructed to avoid eating or drinking about 20 minutes before or after their buprenorphine dosing in order to not

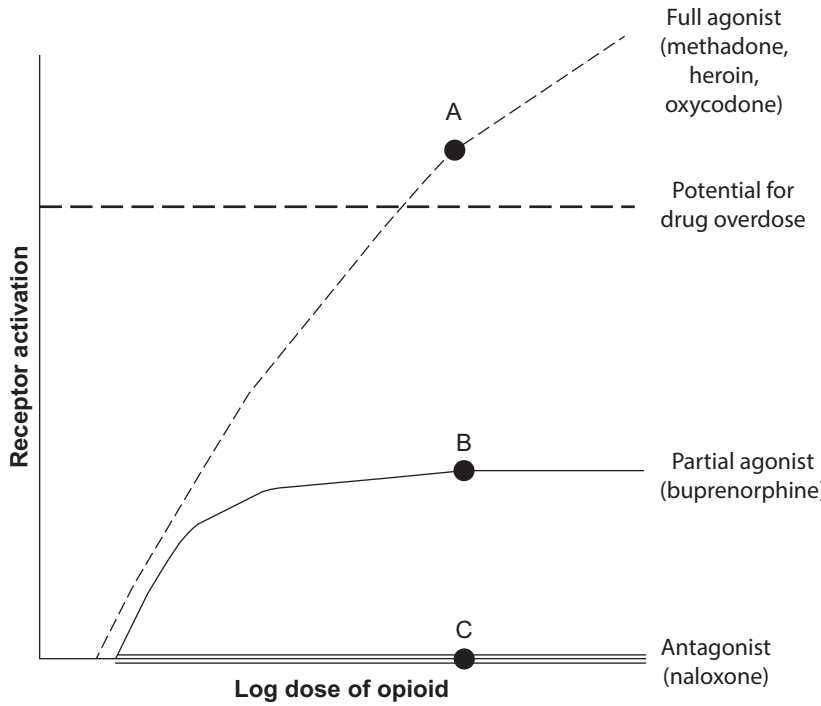

Figure 5.4 Opioid receptor activation versus dose of opioid.

wash away the medication with saliva, as this would lower the dose of medication their body receives.

Long-acting injectable buprenorphine for monthly administration (that is not formulated with naloxone) is also available as 300 mg/injection loading doses and 100 mg/injection maintenance doses. This formulation can be very beneficial for patients who have trouble with daily sublingual medication compliance or for cases of concern for diversion (it is virtually nondivertible) like in prison settings. Once a patient is on a steady dose regimen of injectable buprenorphine (3–4 months) the drug will persist for a remarkably long time in the patient's body, while declining but remaining detectible and active for 6 months or more after a final injection is delivered. This attribute makes this formulation interesting as a pathway for some patients to gently wean off buprenorphine without getting into extreme phases of acute opioid withdrawal.

Patients starting on either methadone or buprenorphine should ideally be in some degree of opioid withdrawal at treatment initiation (to help ensure there are no untoward mixed pharmacological effects of multiple opioids). But this precaution is more significant for buprenorphine, because unlike methadone it can force opioid users into a paradoxical withdrawal. Accordingly, patients initiating buprenorphine (especially for the first time) should undergo programed DWT treatment for 2–4 days prior to first dosing, which should happen in a monitored way in the clinic with check of vital signs and withdrawal levels (e.g., with COWS) before and after dosing. There are at least three major advantages of buprenorphine over methadone as a replacement therapy: First, the treatment is more amenable to incorporating into broader array of individualized care and addiction psychiatry treatment services (consistent with the 2×4 model approach) in which a wide range of co-occurring mental illnesses and addictions can be treated alongside the opioid addiction. Second, patients in a stable pattern of recovery and treatment on buprenorphine can be reliably seen once every 4–8 weeks (avoiding the considerable effort required in methadone programs of patients getting their medication doses in person at the clinic many times a week). Finally, although the evidence base and standard of care clearly indicates that pregnant women with opioid addiction should be on opioid replacement therapy (to minimize the risk of the uncontrolled disease for the mom and the baby), accumulating evidence indicates that buprenorphine is less likely to produce **neonatal abstinence syndrome** (drug withdrawal) for babies after delivery.

Nicotine replacement therapy (NRT) includes a variety of FDA-approved methods of delivering nicotine that avoid (a) the disease-causing impact of smoking on the lungs and (b) the mass toxicological and carcinogenic impact of hundreds of ingredients of tobacco. So, with NRT, the nicotine (which is the extremely addictive ingredient of tobacco) is delivered in pure form into the bloodstream via transdermal patch, gum, lozenge, inhaler, and nasal spray. Although these products are often marketed as short-term stepping stones to fully remitting nicotine addiction (via treating short-term nicotine withdrawal syndrome), they are often not greatly effective as cessation agents on their own. In fact, many patients should consider attempts to convert their nicotine use away from smoking or chewing tobacco products onto NRT as a long-term plan (months to years) that will eventually lead to more decisive FR

treatment strategies. This is an example of how HR and FR strategies should be considered as complimentary strategies that can and should often be sequentially implemented (for a given addiction). Of note, many companies have marketed various inhaled nicotine vaping products as a form of NRT (in the HR vein). However, the evidence does not support this claim and addiction psychiatrists should not condone these products as legitimate treatment tools, as mounting evidence is revealing that they do produce averse pulmonary effects. In teenagers they readily cause new incidences of nicotine addiction that will often lead to tobacco use in oral and smoked forms later on.

Harm Amplification and Misapplication of Harm Reduction Strategies

As an approach that is quite the opposite of evidence-based HR strategies, **harm amplification** is an approach often used by the criminal justice system to punish people with addiction and dual diagnoses in hopes it will reduce addiction-related behaviors and ultimately drive the disease away. This approach is based on the concept of **negative reinforcement**, in which delivery of a negative reinforcer (an unpleasant stimuli or punishment) is intended to direct motivation or behavior toward a more desirable goal. However, although negative reinforcement can modify behavior, it is a relatively poor reinforcer (compared to **positive reinforcement**, which uses desirable/gratifying rewards to sculpt behavior). Thus, harm amplification is not nearly as effective, for example, as certain forms of contingency management (reviewed above, which provides positive reinforcers to people succeeding in recovery). Negative reinforcement also tends to create evasive behavior, not necessarily toward a desired goal, but nonspecifically toward *any goal* as long as it is away from the source of the punishment. Thus, a professional or agency working with a patient that is using harm amplification as a strategy to reduce addiction tends to drive patients away. Harm amplification also works in contrast to evidence-based methods of motivational interviewing in which the clinician is deliberately attempting to *not judge* or use words or interactions that could be stigmatizing, humiliating, or dehumanizing for the patient (which is a form of punishment). Indeed, given that punishment is a form of psychological stress, and given that stress is a major

well-known trigger/inducer of relapse in patients with addiction, different forms of harm amplification can actually drive patients further into "the arms" of the addiction.

There is no other disease of the body or brain other than addiction for which public resources, policy, and legal codes are so heavily invested in the false notion that punishment is a legitimate treatment. To be sure, criminal acts can happen when people are pursuing drugs, using and intoxicated, and the sale and trade of certain illicit drugs and prescription psychoactive/addictive substances, outside of appropriate medical supervision, standards of care, and licensure, should be appropriately investigated, prosecuted, and addressed via the penal system. However, the criminal justice system is not trained for, purposed for, or equipped to provide science-based standards of care for addiction and mental illness. Yet, the lack of an excellent, widely accessible national professional workforce and treatment infrastructure for addiction psychiatry has essentially forced the criminal justice systems in many areas of the United States into being the dominant or only agency available for addressing mental illness and addiction (however ineffectively). Punishing addiction via mass incarceration, financial penalties, removing health insurance eligibility (which incarceration causes), criminal-record branding (drug-related felony records often prevent employment or eligibility to live in safe or decent housing) as enacted in the "War on Drugs" has not proven effective at preventing or treating addiction. In some ways these harm-amplification strategies may actually have unintended consequences of perpetuating conditions that contribute to mental illness and addiction, while sucking needed resources away from legitimate science-based treatments, treatment workforce, infrastructure, and services.

Other strategies for addiction or mental illness treatment that are of a biomedical form and that could be framed by proponents as HR approaches may actually not qualify as such because the evidence base in support of them is too sparse, unclear, weak, or biased. Given that there are legitimate and thoroughly scientifically supported HR strategies for using certain opioids (methadone and buprenorphine) for opioid addiction, or nicotine for nicotine addiction, it is tempting to believe that the same principal could apply across all addictive drugs (e.g., give alcohol for alcohol addiction, cocaine for cocaine addiction, amphetamines for amphetamine addiction, THC for THC addiction,

and so on). However, this is not the case. The weight of available evidence does not support this approach as a universally good strategy across all addictive drugs. This is because different addictive drugs are differentially addictive, have different intoxicating profiles, routes of entry, and different long-term medical and psychiatric consequences. We also have a medical system (particularly in the United States) that is significantly market-seeking, advertising-driven, and profit-motivated. Accordingly, this system has a track record of being vulnerable to a tendency toward selling addictive drugs to patients at levels, and for indications, beyond what the evidence-base truly supports. Areas of controversy along these lines include the advocacy of medical cannabis for psychiatric disorders or addiction. Although some THC and natural cannabis products may be relatively safe recreational drugs, and their use should clearly not be criminalized (e.g., because criminalization can produce more harm than the drug itself), the evidence shows these drugs are also addictive and mostly liable to worsening (not treating) virtually all forms mental illness. Similarly, prescribing amphetamines for amphetamine or cocaine addiction has gained some traction even among reputable academic sources, but the weight of the existing basic or clinical evidence still does not yet support the use of these drugs as legitimate HR strategies that should be practiced or condoned outside of well-monitored research contexts. The prescribing of benzodiazepines chronically (without a taper) as an attempt to substitute for alcohol, benzodiazepine, or barbiturate addictions is also not well supported by the evidence base, even though these flawed and dangerous strategies are often pursued.

The use of HR-like strategies that are not adequately supported by science reflects a key vulnerability within healthcare systems, particularly the American one, that sometimes arise from the prioritization of profit motives beyond the restraints and guidance of medical evidence or well-conducted longitudinal scientific studies. This problem is magnified by the fact that behavioral health is a relatively resource-impoverished and stigmatized sector of health care, even as well-designed clinical trials in psychiatry and addictionology can be expensive to conduct. Unfortunately, also, new drug treatment research and development regulated and supported by federal agencies including the FDA and the NIH (including the siloed behavioral health divisions of NIDA, NIAAA, and NIMH) tend to promote medication development and commercialism for very narrow,

single-illness indications based on clinical study designs that largely ignore or avoid the clinical realities of high rates of addiction and mental health comorbidities (i.e., they tend to support studies that exclude and discriminate against dual-diagnosis patients). Thus, our current systems and cultures for treatment research and development are not well suited or resourced for helping us understand how a given treatment being studied for one psychiatric indication, or addiction, may help *or exacerbate* another psychiatric indication or addiction that is often found in comorbid combinations. To best account and respond to these complex issues in the most clinically and ethically sound way, and to protect the primacy of scientific evidence as the key guide for clinical standards and decision-making, the authors suggest that the field of addiction psychiatry should follow these guidelines on pharmacology across its clinical, training, and research missions:

(1) **Avoid chronic polypharmacy prescribing of controlled addictive medications.** If a patient must be on a chronic regimen of a controlled substance (e.g., buprenorphine) then avoid prescribing the patient a second controlled substance regimen (e.g., from the benzoid, stimulant, or THC classes) on a long-term basis or in a replacement therapy rationale.

(2) **When prescribing a controlled substance of any kind, stay within the bounds of the approved FDA indication set and evidence-based dosing.** Although "off-label" applications of nonscheduled medications (drugs not classified as controlled substances by the DEA) is commonly done with good rationale (as supported by an evidence base), the prescription of controlled drugs (opioids, benzoids, and stimulants) for off-label uses, doses, or durations outside of FDA recommendations should be avoided.

(3) **Avoid providing or selling experimental treatments (treatments without clear, well-replicated scientific evidence) to patients outside of a research context or protocol.** An addiction psychiatrist who is prescribing any medication (controlled or not) or treatment modality that is novel, not FDA-approved (for the target indication), and not yet well-supported by a replicated evidence base should be approaching that clinical application as a research enterprise in which there is some degree of oversight, informed consent, and intent to report the results to a peer-reviewed biomedical journal.

(4) **When conducting treatment research and development for patients with addictions, attempt to conduct the case study, case series, or large sample-controlled trials following a 2×4 model (integrated addiction psychiatry)-informed approach.** This means that for any given patient-subject being treated by an experimental drug for a mental health or an addiction indication, dual-diagnosis (comorbid) patients should not be systematically excluded or discriminated against from entering the study, and multiple outcomes should be tracked pertaining to *both* mental illness and addiction-related symptoms and behaviors.

Integrating and Sequencing Harm Reduction and Full Remission Treatments in One Treatment Plan

In addiction psychiatry clinics, it is perfectly acceptable and often best to integrate both HR and FR treatments. For a specific target drug the patient is addicted to, this might mean first stabilizing the patient with an HR treatment *to contain and control the addiction*, then second, transitioning the patient to an FR treatment in an attempt *to totally eliminate the addiction* (where they no longer ever use any drug of that class). For example, a patient may transition from methadone replacement therapy to naltrexone treatment with the goal of total cessation of all opioids. It is sometimes the case, and also totally OK, that patients will actually bounce back and forth between HR and FR strategies for a given addiction until they hopefully land on an FR treatment. In fact, it can help embolden a patient to attempt an FR treatment if they know they have an evidence-based HR treatment to fall back on. It is also possible and common for patients to be struggling with multiple addictions (to different drug types) at the same time. In this situation it is also acceptable and often desirable for the patient to be pursing an HR approach with respect to one addiction and an FR approach with another. For example, they may be on buprenorphine for opioid addiction (an HR approach) while taking bupropion in an attempt to eliminate all forms of nicotine addiction. Table 5.7 outlines the current FDA-approved medications used in HR and FR strategies for substance-use disorders.

Full Remission Treatments: Eliminating the Monster

Full remission treatments (*abstinence* or *cessation* treatments) utilize a pharmacology or other biological intervention that *does not* replicate

Table 5.7 FDA-approved medications used in HR and FR strategies for substance-use disorders

Medication	FDA-approved diagnosis	Mechanism of action	Most notable side effects
Methadone (Dolophine, Methadose)	Opioid-use disorder	Full opioid receptor agonist	Respiratory depression, CNS depression, QT prolongation, hypotension
Buprenorphine/naloxone (Suboxone, Zubsolv, Bunavail, Cassipa)	Opioid-use disorder	Partial opioid mu receptor agonist/mu opioid receptor antagonist	Respiratory depression, CNS depression, hypotension
Naltrexone (Vivitrol, Revia, Depade)	Opioid-use disorder, alcohol use disorder	Opioid receptor antagonist	Nausea, headache, insomnia, hepatocellular injury, precipitating opioid withdrawal
Acamprosate (Campral)	Alcohol-use disorder	Interacts with glutamate system	Diarrhea
Disulfiram (Antabuse)	Alcohol-use disorder	Inhibits alcohol dehydrogenase	When combined with alcohol: vertigo, syncope, confusion, respiratory depression, cardiovascular collapse, liver failure
Nicotine replacement therapies (Nicoderm CQ, Nicotrol)	Tobacco-use disorder	Full nicotinic receptor agonist	Increased heart rate and blood pressure, dizziness, insomnia, anxiety, nausea
Varenicline (Chantix)	Tobacco-use disorder	Partial nicotinic receptor agonist	CNS depression, nausea, headache, insomnia, somnambulism, depression, suicidal ideation, seizures
Bupropion (Wellbutrin, Zyban)	Tobacco-use disorder	Norepinephrine dopamine reuptake inhibitor	Headache, irritability, anxiety, tremors, weight loss, insomnia, seizures

the pharmacology of the addictive drug (which would make the treatment a replacement/HR type treatment), with the goal of completely terminating all use of drugs in the target drug class. This treatment is often the ultimate goal of addiction treatment, much as remitting a cancer is the ultimate goal of oncology. However, as we also know from oncology, cancers can return after an initial phase of remission, and so it is with addiction. As mentioned above, patients under these circumstances may have to return to HR strategies to stage toward another FR treatment attempt. Or they may elect with their physicians to stay in an HR approach indefinitely as the best option. Generally, FR is more difficult to achieve (for both clinicians and patients alike) compared to maintaining in an HR approach. However, FR is more decisive in achieving what can be viewed as essentially a full cure, in which the patient not only will never experience more harm from seeking or using the drug again, but will also not have to be indefinitely tied to effort, responsibility, and expenses that ongoing HR treatment must entail.

Full remission treatments do not necessarily refer to a specific medication for a given addiction indication, because FR treatment strategies can (and should often) be composed of both medications, psychotherapies, and experiential treatments (an integrated treatment strategy) for a given patient. In fact, there are some types of addictions for which we have yet to develop a clearly efficacious medication strategy that is FDA-approved for that drug indication (e.g., cocaine addiction, amphetamine addiction, cannabis addiction). In these situations, the core FR strategy for the specific addiction may be psychotherapeutically based, and the medications are there primarily to target other comorbidities, or used off-label from their FDA indications in hopes it will treat the main addiction (e.g., using bupropion or topiramate to treat amphetamine addiction). Nevertheless, for the list of medications that sit squarely in the lane of FR treatments (naltrexone, acamprosate, bupropion, varenicline) and have FDA indications for specific addictions, the goal of those meds is to impact the addiction disease biology in a therapeutic way without substituting for the addictive drug as in HR treatments. But even with this difference in treatment aims, medications that serve as FR treatments and those that provide HR treatments (e.g., compare naltrexone versus methadone) can have quite similar efficacies, principally in reducing subjective craving and objectively in reducing drug-seeking behavior and use over time. Specific FR treatments for addiction are outlined below.

Full Remission Treatments for Nicotine Addiction

Nicotine stands as one of the most addictive and deadly drugs (especially when smoked or used in tobacco forms) known to man. Unfortunately, its ubiquity, its lack of impairing intoxication, its history (as tied to the early economic development of the United States), its mischaracterization as a "medication" for mental illness (see Chapter 2 Myth-Busters), its relative social acceptance, and so on, all make it easy for clinicians and even addiction psychiatrists to forget to diagnose, track, and treat nicotine addiction. Nevertheless, helping patients remit nicotine addiction can be one of the most impactful interventions a physician can do for their patients to prevent horrific secondary disease consequences, to add many years to their life spans, and save them thousands of dollars. At the present time there are two FR pharmacological treatments for nicotine addiction: bupropion and varenicline, each with different strengths and weaknesses. It can be helpful to approach the start of either of these treatments with an initial run of some form of nicotine replacement therapy (HR with nicotine products). In addition, prescribing these medicines should be accompanied by an eclectic psychotherapeutic approach that combines supportive psychodynamic, MET, and CBT elements. Experiential changes should also be implemented as much as possible (e.g., asking still-smoking family members to smoke outside and not in front of the patient; having the patient start a consistent aerobic exercise regimen). For initiating either of these medications, the physician should first work with the patient to establish a firm quit date that is intended to be the first full day of not using any form of nicotine. Generally, the patient will start with lower doses of the medication (bupropion: 100–150 mg a day; varenicline 0.5 mg Q day or 0.5 mg BID) for a few days or weeks prior to the quit date (to test tolerability and see how the med may spontaneously decrease nicotine use). Then the doses should be raised to the high-optimal levels on the quit date (bupropion: 150 mg BID or 300 mg XL in AM; varenicline 1 mg BID). Generally, patients should be directed to stay on either medication for 4–6 months after the quit date, if tolerated and there are few to no relapses to nicotine during this time.

Bupropion is a dopamine and norepinephrine reuptake inhibitor that has several uses including as an FR treatment for nicotine addiction, and

as a treatment for major depressive disorder or seasonal affective disorder. It can also be used "off-label" for ADHD, or stimulant addiction, which is especially useful for those patients where amphetamine and/or cocaine addiction is a concern. It can also help with therapeutic appetite suppression/weight loss, and may reverse some forms of sexual dysfunction that result from taking other psychiatric drugs. At present, bupropion is unique in psychiatry as being a **genuine parsimonious dual-diagnosis medication** (or integrative treatment) in that it can treat (and is FDA-approved to treat) both a type of mental illness (depression) and a type of addiction (to nicotine) without it being addictive itself. The exact mechanism of how bupropion decreases nicotine cravings is not well understood, but it is thought to cause reduced activation of prefrontal cortical–ventral striatal circuits that are associated with nicotine craving. This reduction allows an individual who is actively resisting cravings to have a higher chance of success. The most significant serious side effect associated with bupropion is a reduction in seizure threshold. This risk occurs in a dose-dependent manner, and inversely with the body weight of the patient. At doses up to 300 mg a day, the seizure risk is about 0.1%, which is comparable to most SSRIs. At doses up to 450 mg, risk increases to about 0.4%, and at doses higher than 450 mg a day the risk jumps drastically to 4%. Thus, doses above 450 mg daily should be avoided, especially in underweight individuals. Of note, bupropion is metabolized by cytochrome P450 and is itself a cytochrome p450 2D6 inhibitor, so prescribers should assess drug interactions to avoid unintentionally increasing bupropion levels above the 450 mg daily maximum. Although bupropion can improve symptoms of depression, it can have common side effects of increased anxiety, irritability, and insomnia. It can also lead to a manic episode in certain patients whose mood disorders are more accurately characterized as bipolar as opposed to unipolar (depression) and who are not on mood stabilizers. Like other antidepressants, it also carries a black box warning for risk of increased suicidal ideation.

Varenicline is a partial agonist at the alpha-4-beta-2 nicotinic acetylcholinergic receptor. It works in part by "fooling the brain" into having a "nicotine-satiated" response, like what a cigarette or some other form of nicotine would produce, but without actually delivering nicotine, or without the patient being addicted to varenicline itself. As varenicline

does affect the nicotine receptor, its potential side effects are somewhat like those seen with nicotine: nausea with potential vomiting, headaches, irritability, insomnia, anxiety, and vivid dreams. A patient should not generally combine nicotine replacement therapy products with varenicline when on the maximum maintenance dose of 1 mg BID, because this nicotine use can increase side effects and it basically undermines the therapeutic intent and impact of the varenicline itself.

After varenicline was initially FDA-approved and first widely used, there were emerging concerns about the drug being associated with an increased risk of neuropsychiatric side effects (depression and suicidal ideation). However, further research has reduced this concern, largely attributing these observations to the fact that patients with nicotine addiction often have co-occurring mental illnesses (not so much that varenicline is causing these symptoms). This again is a concrete example of the limitation (mentioned in the HR section above) of our usual approaches and study designs in psychiatric drug development, which often focus narrowly on target indications in patient samples that are relatively devoid of complex psychiatric and addiction comorbidities (and therefore not representative of mainstream "real-world" populations who will eventually be prescribed the drug). Of note, **after marketing studies** of varenicline for people with comorbid alcohol addiction also suggest it may have utility for alcohol addiction, which was also missed in the initial pivotal trials for nicotine. When considering which strategy to try, varenicline versus bupropion, the main factors to consider are differential tolerability, the fact that bupropion is an effective antidepressant (whereas varenicline is not), and that in terms of raw effectiveness against nicotine addiction (with all other factors held constant), varenicline is superior.

Full Remission Treatments for Alcohol Addiction

Alcohol addiction can hide in plain sight more easily than other addictions because it is so widely used in the general population, and it is a large part of the economy spanning entertainment and hospitality industries. Being buzzed or drunk on alcohol on occasion is not necessarily a definitive sign of having alcohol addiction, and being sober from it (or not appearing intoxicated while drinking) is not necessarily evidence that one does not have the addiction. But, due to

the massive multiorgan toxicological and intoxication-impairing effects that chronic heavy drinking can cause, alcohol addiction remains – alongside addictions to nicotine, opioids, and stimulants – a major public health challenge and cause of early death in the United States. In the primary care or psychiatric care setting, common clinical signs that may point to the presence of a previously unrecognized alcohol addiction include: hypertension, insomnia, anxiety, depression, obesity, and cognitive problems. When assessing average drinking levels in patients, clinicians should attend to the "3 to 1 rule," which means that patients will usually minimize and underreport their drinking levels to as low as a third of what they really drink! But of course, understanding absolute drinking levels does not actually directly determine whether or not someone has alcohol addiction, which should be assessed based on DSM criteria (Chapter 2), and a determination of whether they are experiencing one or more negative consequences (medical, legal, occupational, social, psychiatric) that come from compulsive drinking.

At present there are three FDA-approved FR medication treatments for alcohol-use disorder: disulfiram, acamprosate, and naltrexone (oral or long-acting injectable forms). In general, patients should undergo DWT assessment and treatment (for alcohol withdrawal) first in leading up to the initiation of any of these treatments. They can also be combined with each other fairly safely, although evidence for added efficacy when they are combined is sparse. Patients in the early course of treatment should be advised to stay on these medications even if they are still relapsing onto bouts of drinking, because these treatments can still reduce overall alcohol use even when someone has not achieved full sobriety.

Disulfiram is unique in the FR medication world not only because it is the oldest anti-addiction drug (starting in the 1940s), but because it acts uniquely as a kind of pharmacological harm-amplification strategy. Disulfiram literally produces a punishing effect on the patient if they drink. Ingesting even small amounts of alcohol while taking disulfiram (e.g., even accidentally via certain foods, mouthwash, and so on) can make the patient quite sick with nausea, vomiting, flushing, headache, dysphoria, tachycardia, hypotension, palpitations, and anxiety. Thus, it induces a syndrome somewhat like what people experience with a severe hangover. However, the reaction can happen very quickly, within minutes after alcohol intake. Disulfiram creates this effect by interfering with

normal alcohol metabolism. Normally, alcohol is metabolized by the body into acetaldehyde (by alcohol dehydrogenase), which is then metabolized further by the enzyme acetaldehyde dehydrogenase. Disulfiram inhibits acetaldehyde dehydrogenase, which causes (when someone is ingesting alcohol) acetaldehyde to rapidly build up in the bloodstream – which makes people feel very sick. Working primarily as a negative reinforcement strategy that patients must be fully aware of and consent to, disulfiram is not particularly effective. If a patient is planning on a relapse, all they have to do to avoid getting sick is to skip their disulfiram dosing. Some patients with severe alcohol addiction will even drink on top of disulfiram despite getting sick in a vivid illustration of the core definition of addiction: compulsive drug use despite negative consequences. But even with these downsides, disulfiram can still be useful in some patients who are disciplined and highly motivated. It can work as a good adjunct medication for patients on other anti-alcohol medications on a temporary basis, like if a patient is anticipating encountering a highly triggering situation or context (e.g., holidays, parties). Disulfiram can cause an acute hepatitis (which is already a risk for patients with alcohol addiction), so liver monitoring is prudent. Patients should be educated about the signs of liver failure, such as yellowing of the eyes, very dark urine, fatigue, and nausea. Disulfiram should be avoided in patients with significant cardiovascular disease, or those above 60 years of age, due to the stress that acetaldehyde reaction can have on the heart and vascular system.

Interestingly, there is some evidence that disulfiram may potentiate endogenous DA neurotransmission in the ventral striatum. This effect might allow the drug to be useful for some patients as a treatment for stimulant addiction, although this is not an FDA indication and more clinical studies are needed to test this possibility. Regardless, acute psychosis is an additional noteworthy side effect of disulfiram that may be associated with its effect on dopamine transmission.

Acamprosate is an anti-alcohol addiction drug that works to suppress alcohol craving, relapses, and for some patients, the extent of relapses. It does this not by punishing the patient (it does not interfere with or amplify alcohol intoxication or withdrawal) but apparently by disrupting the brain circuitry that mediates stimuli-induced craving and relapses. Precisely how acamprosate does this is not well understood, although it likely involves effects on the glutamate neurotransmitter

system where it acts as a mild NMDA receptor antagonist. The drug may also have effects on a different class of GLU receptors (metabotropic receptors) and indirectly on the GABA transmitter system, all of which are pathologically altered by chronic heavy alcohol consumption. Acamprosate is FDA-approved for alcohol-use disorder in patients who are abstinent at the time of treatment initiation. It requires large and frequent dosing of 666 mg (2 × 333 mg pills) three times per day in order for the drug to substantially get through the blood–brain barrier. This dosing can be challenging for patients who struggle with medication adherence. The drug's most notable symptoms involve the gastrointestinal (GI) system, including diarrhea, flatulence, and nausea. Encouraging patients to take it with meals may help increase adherence and reduce the chance of GI side effects. A major advantage of acamprosate is that it is metabolized by the kidneys only and is essentially invisible to the liver. So, it does not carry risk to the liver for patients with liver disease or elevated risk of hepatitis. The downside of acamprosate (other than its challenging dosing schedule) is that it is probably not as effective overall for most people as is naltrexone.

Naltrexone, an opioid receptor antagonist, stands as the most generally effective medication against alcohol addiction, with an action that is similar to what has been characterized for acamprosate in blunting trigger-induced craving and lowering the frequency and durations of relapses. The efficacy of the drug for alcohol addiction, even though its mechanism is focused on blockade of opioid receptors, speaks to the involvement of opioid receptors (and the motivational circuits they regulate) in several forms of addiction beyond those directly involving opioids. Thus, naltrexone also has some efficacy as an appetite suppressant (as a putative anti-"food addiction" medication) and for certain other compulsive behaviors or behavioral addictions like pathological gambling. Naltrexone, like acamprosate, is a genuine anti-addiction medication that also does not rely on a negative reinforcement (harm-amplification strategy). So as with acamprosate, people on naltrexone can drink alcohol and get intoxicated without getting sick. However, many patients do report a subjective sense that the naltrexone limits the good feeling or mild euphoric buzz that happens in the initial moments of alcohol intoxication. Both the daily oral formulation (~50 mg a day) and the monthly intramuscular formulation (380 mg/month, brand name Vivitrol) can be used to treat alcohol addiction. Generally, if

patients can tolerate receiving the shot, this is the better approach because it is less prone to side effects, including liver toxicity (probably due to more stable pharmacokinetics with the steady intramuscular release). This modality is also less susceptible to intermittent breakdowns in compliance that often come with trying to maintain consistent daily oral intake of any medication. Again, because chronic alcohol use causes liver damage, and naltrexone can also (rarely) stress the liver, liver function is important to assess around the initiation of treatment and intermittently thereafter. Patients should generally be started on naltrexone after they have undergone DWT to maximize the therapeutic value of the medication and reduce risk of side effects. However, if there is evidence that the medication is working for them (to reduce and significantly limit relapses) they should be encouraged to stay on it steadily even through limited relapses.

Full Remission Treatment for Opioid Addiction

Naltrexone is also currently the mainstay of FDA-approved FR pharmacological treatments for opioid addiction. In contrast to alcohol addiction, there is a much bigger gap in the comparative efficacies of oral naltrexone versus the long-acting injectable formulation (Vivitrol). The latter is by far more effective and decisive compared to the oral formulation, particularly in the early months of opioid addiction treatment. This has to do with two main factors including the long-acting efficacy of the IM injection (lasting 4–5 weeks, which removes the issue of variable daily medication compliance) and the capacity of the injectable formulation to not be thwarted or reversed by a patient who is planning an opioid relapse. Vivitrol is thus not liable to the deliberate disruption in treatment that is the Achilles' heel of disulfiram treatment for alcohol addiction. Also, in the case of opioid addiction (in contrast to alcohol addiction), naltrexone has a strong effect in blocking the high (or any other pharmacological effects) that opioids (when taken in typical dose ranges) produce. So, for 4–5 weeks after a patient is given Vivitrol, they really cannot turn off the medication, and most relapses that they may have during that period of time are relatively inconsequential – a waste of time, money, and effort from the standpoint of the opioid-addicted brain. Many patients with opioid addiction on Vivitrol do experiment with an opioid relapse or two and confirm for themselves

that relapse is hard to do on the medication even if it is their intent in the midst of a "craving storm." Now, the flip side of this effect is if a given patient on Vivitrol is truly in need of opioids despite their addiction (e.g., in the context of needing pain relief after suffering a major injury or being postoperative) then an "opioidergic override" of the naltrexone is possible. But that should be done only under direct medical supervision in an emergency room or inpatient setting.

Naltrexone can shield against the pharmacological effects of opioids in a quite comfortable, side effect–free way if the patient is on stable doses of the medication prior to a relapse. However, the same is not true if the order is reversed, that is, if a patient is on a chronic regimen of an opioid and then suddenly takes naltrexone. In this circumstance, the naltrexone delivery can cause a sudden, severe, and quite adverse **opioid-antagonist–induced opioid withdrawal syndrome** (OWS). **Naloxone**, the very short-acting opioid blocker (used to reverse overdoses or to accompany buprenorphine formulations), can also do this, but its OWS effects are relatively brief. Oral naltrexone with activity for up to 20 or more hours can produce a much more long-lasting and severe OWS. Even more extremely, Vivitrol is so long-lasting (weeks) that it can force a patient into a pharmacological OWS that is quite comprehensive, severe, and relatively prolonged. If given before or without providing DWT in opioid patients who have not yet entered OWS, Vivitrol can essentially force patients into enduring OWS through to its completion. Many patients' reaction to naltrexone under these circumstances would be to reject any future doses of the medication. For this reason, it is critically important for patients with opioid addiction going onto Vivitrol to be treated first with DWT (that does not involve using opioids) and as far as possible through OWS. In fact, FDA guidelines suggest that patients be totally free of any opioid for at least 7 days prior to receiving a Vivitrol injection (including illicit opioids, opioids prescribed for pain, methadone, or buprenorphine, and so on). The need for patients to undergo medically guided passage through and treatment for most if not all of OWS (or at least the peak of it, which occurs within 3–7 days) is thus much more important for naltrexone/Vivitrol than when inducing patients on methadone or buprenorphine. For this reason, most patients are typically much more interested in buprenorphine at the start of long-term treatment, while delaying or avoiding the ordeal of going through the substantial OWS sickness that

must come with initiating Vivitrol. However, when compared head to head, after OWS has been treated, buprenorphine and vivitrol treatment have comparable efficacy in blunting craving and relapses. In the long term, only Vivitrol can facilitate full illness remission, often within 6 months to a year, in which case the patient may never have to suffer OWS again (if they do not re-acquire a chronic pattern of opioid use). Because enduring OWS is such a major barrier for many patients in going into FR treatment with naltrexone, the discovery of new treatments for opioid-antagonist–induced OWS is an important area of research.

Full Remission Treatments for Benzoids

We adopt the term **benzoids** to refer broadly to the range of controlled sedative–hypnotic drugs that work by agonizing or potentiating the activity of the $GABA_A$ receptor. This group of drugs includes the benzodiazepines (e.g., lorazepam, alprazolam, midazolam, diazepam, clonazepam, chlordiazepoxide, temazepam), the "atypical" benzodiazepines (e.g., pregabalin, zolpidem, eszopiclone), and barbiturates (phenobarbital, pentobarbital, propofol). They are all capable of producing physiological dependence with a number of desirable acute effects (antiseizure, anti-anxiety, anti-insomnia) versus undesirable effects (motor impairment, memory lapses, cognitive impairment, behavioral disinhibition, risk of overdose when combined with other CNS depressants). Dependence sets in with chronic use to these drugs: tolerance builds against the acute desirable effects while the patient becomes increasingly vulnerable to major withdrawal, which produces the opposite of the acute desirable effects (seizures, extreme anxiety, insomnia, elevated heart rate). In general, the medical risk of these three drug subclasses, in terms of lethal overdose, are mild to medium for benzodiazepines and atypical benzodiazepines, and major for the barbiturates. However, if benzodiazepines are mixed with opioids, alcohol, or barbiturates, their potential for producing dangerous/impairing intoxication and lethal overdose is significantly enhanced.

All benzoid drugs can produce addiction-like patterns of habitual use and many adverse effects when taken long term that *often* end up being worse than the original symptoms (e.g., of anxiety, insomnia) the drugs were intended to treat. So, these drugs should *generally not be prescribed long term to anyone for any psychiatric indication*, except in rare cases with clear and exceptional justification, and only in the absence of controlled

substance polypharmacy or alcohol use. We use the term *addiction-like* patterns for these drugs because for most patients, if you can get them successfully through the withdrawal syndrome via effective DWT, they do not usually show long-term craving or other signs of motivational damage typical of other major addictions (to nicotine, alcohol, cocaine, amphetamines, opioids, and so on). In other words, these drugs are among the least addictive of the fully or semi-addictive drugs we encounter in addiction treatment. So, if the clinician designs an effective DWT regimen (with the use of a well-designed, long-acting benzodiazepine taper and other adjunct medications), there is a relatively high chance of success in achieving full sustained remission. Thus, FR treatment of benzoid use disorders is pretty much the same as DWT treatment (involving a well-controlled, medically supervised benzodiazepine taper happening over days up to a few months). This hybridized DWT/FR treatment of benzoid use disorders, when done with expert supervision, psychotherapeutic support, and the use of noncontrolled prescription medicines to treat insomnia and anxiety, can usually be done quite successfully on an outpatient basis for most patients who do not have other major addiction comorbidities.

Full Remission Strategies for Stimulants (Amphetamines and Cocaine) and Cannabinoids

Unfortunately, due to a combination of scientific challenges and deficiencies of research investment, we do not yet have strongly effective, FDA-approved pharmacological treatments for addictions involving amphetamines, methamphetamines, "bath salts" (cathinone family compounds with amphetamine-like pharmacology), cocaine, or cannabinoid-spectrum compounds. However, as the healthcare system has increasingly endorsed a wide range of rationales and indications for the use of many of these drugs as treatment agents, there is a growing need to identify and treat addictions to these drugs. Fortunately, our basic science understanding of how these compounds produce addiction (and their various psychotogenic and motivational effects) is continuing to advance very quickly, and it is likely that significant breakthroughs in the medication management of these addictions will emerge. As of now, the mainstay of methamphetamine/amphetamine and THC-spectrum addiction is MET-based psychotherapy with adjunct medications for co-occurring mental illness and other addictions. There is some

scientific evidence suggesting the therapeutic value of a range of medications specifically for stimulant addictions (e.g., mirtazapine, bupropion, disulfiram, tricyclic antidepressants, *N*-acetylcysteine, topiramate) in certain patient samples, and it is possible that one or more of these treatments, perhaps in combination with other agents, will be proven effective or eventually gain FDA approval.

Full Remission Strategies for Special Drug Use Disorders and Behavioral Addictions

We use the phrase "special drug-use disorders" to mean the chronic/harmful use of a range of hallucinogenic drugs (e.g., lysergic acid diethylamide (LSD), psilocybin, phencyclidine (PCP), ketamine), various classes of inhalants (gasoline, glue, nitrous oxide), or mixed-effect designer drugs (e.g., methylene-dioxy-methamphetamine (MDMA), aka "Ecstasy"; mitragynine (aka "kratom")). As a group, the pharmacology of these drugs is quite diverse and complex, and they *tend* to have robust and vivid intoxicating effects that outstrip their addictive effects. This is especially true for the hallucinogens, which are not really addictive. However, people can absolutely get into strong addictions involving designer stimulants, inhalants, and phencyclidine, although ketamine and mitragynine pose more moderate addiction risks. MDMA, although being structurally similar to the amphetamine molecule and carrying an interesting intoxication profile (capable of stimulating a sense of empathy and interpersonal connectedness, and some significant hyperthermic safety risks) is also not strongly addictive. Mitragynine, with its stimulant-like effects at low doses and opioidergic properties at higher doses, carries greater addiction liability than MDMA. As yet, there are no FDA-approved FR medication treatments for addictions to any of these drugs, although naltrexone and various off-label treatments (listed for the stimulants in the prior section) are being studied.

As reviewed in prior chapters, behavioral addictions (pathological gambling, compulsive shopping, shoplifting, internet/gaming addictions, compulsive sexual behavior, and so on) are often comorbid with and share much of the same neurobiology and clinical phenomenology as substance addictions. Unfortunately, research funding support for behavioral addictions is generally lacking, and new medication development for addiction is almost totally focused on chemical addictions. Accordingly,

new treatments (medications or psychotherapies) for behavioral addictions will likely continue to be borrowed and adapted from much larger-scale lines of chemical addiction research.

New Frontiers in Addiction and Dual-Diagnosis Research

The *neuroscience of motivation*, as introduced across the chapters of this book, is an exciting and rapidly advancing field of biological and computational (i.e., neural network) neuroscience that is related to and has implications for many other fields beyond addiction psychiatry, including economics and computer science/artificial intelligence. As this area of research progresses and given the massive and still growing adverse impact addictions (a primary disease of motivation) have on mental health and public health, we can expect motivational neuroscience to inform the development, testing, and production of many new, ground-breaking diagnostic approaches and treatment strategies in the decades ahead. Based on the foundation of already existing evidence-based treatments covered in this chapter, we can expect that future advances will incorporate themes and concepts as outlined below.

Diagnostic innovations in addiction psychiatry can be expected to evolve into a range of new technologies that better characterize subpopulations, disease risk factors, comorbidities, severities, and stages of diseases that can indicate more specific and customizable preventative or therapeutic approaches. Although **neuroimaging** (i.e., anatomical and functional brain scanning) is not likely to be useful by itself as a general screening or diagnostic tool for addiction, it may eventually form part of a suite of diagnostic tools, to be incorporated along with biomarker assays or cognitive/impulsivity testing for estimating addiction risk in young people to guide decisions about preventative interventions. **Multimodal testing suites** like this may also guide medication and neuromechanical treatment choices for older patients with more advanced stage forms of addiction. Neuroimaging may also soon play a role in allowing personalized, neuroanatomically specific therapeutic interventions like deep brain stimulation or focal

delivery of bioactive particles, allowing precision targeting of circuits that are pathologically supporting drug cue-triggering of urges and craving. **Pharmacogenomics** is a frontier of clinical research where analysis of an individual's genetic makeup could guide treatment decision-making. This approach and analysis of a wider range of other biomarkers (e.g., neurohormonal levels including corticosteroid stress responsivity, and oxytocin dynamics) may be used in conjunction with phenotypic measures of comorbid psychiatric illness or specific psychological trauma histories, to better match addiction disease "flavors" with specific integrative treatment combinations. Treatment outcome measurement is also expected to become more objective, more temporally precise, and more automatic with the advent of wearable technologies and data tracking systems. **Remote clinical telemetry** could, for example, automatically relay to the treatment team a daily summary of a patient's motor activity, sleep cycle, and addictive drug–specific relapse information. In turn, this information could be automatically summarized, analyzed, and periodically reviewed by the addiction psychiatrist with the patient during clinical appointments to assess treatment plan efficacy. Wearable technology that could detect drug levels transdermally, based on recent developments in glucose monitoring for people with diabetes, is an exciting frontier for addiction treatment outcome research.

Medication innovations in addiction psychiatry are expected to continue to occur along the emerging frontier of research on **psychoactive neuroplastogens**. Some of the drugs already mentioned in the "special drug-use disorders" section (e.g., LSD, psilocybin, MDMA, and ketamine) are of interest in this vein as they encompass unique intoxicating profiles and potentially beneficial *neuroplastic* effects, without introducing serous risks of addiction. For example, intranasal delivery of the enantiomer of ketamine (esketamine; an NMDA-GLU receptor antagonist that produces neuroplastic effects that are different from traditional antidepressants) has gained a firm evidence base and FDA approval for the treatment of major depression. Esketamine is now being investigated for a broader array of indications on the dual-diagnosis spectrum including alcohol and opioid addictions.

Much of the cutting-edge research on psychoactive neuroplastogens is exploring the use of these drugs as **phasic treatments** (delivered over

a short period of time at specific stages or transition points of recovery) and as **integrative treatments** (that could target more than one indication, or that can be delivered more effectively for one indication when combined with other treatment modalities). Bupropion, already mentioned above as a **parsimonious dual-diagnosis agent**, is one prominent example of a nonphasic yet integrative medication treatment that can treat both an addiction (to nicotine) and a mental illness (major depression) and is often more efficacious when delivered with a psychotherapy. Given the many neurobiological and clinical ways that mental illness and addictions are interconnected and exist as integrated disease processes, it can be expected that more new treatments will have multiple efficacies that span addiction and mental illness syndromes. Addiction psychiatry clinics that operate consistent with the 2×4 model design, in which both mental illness and addictions are diagnosed and treated with equal priority and expertise in a way that integrates medication and psychotherapeutic modalities, will be ideal settings for advancing the discovery, development, testing, and utilization of novel integrative treatments.

Innovations in neuromodulation treatments including **rTMS (repetitive transcranial magnetic stimulation)** and its variants may also be used as phasic and integrative treatments for addiction and various other dual-diagnosis conditions. TMS, which is already FDA-cleared for the treatment of nicotine addiction, uses highly focused electromagnetic wave pulses that cause specific regions of motivation-related neural networks to activate or fatigue. This treatment may be applied while the patient is remaining passive or is participating in generating an internal representation of an experience that is understood as contributory to the problem (e.g., a trauma memory, negative rumination, craving). Either way, rTMS aims to alter the way the target network (that is involved in the pathological cognition, emotion, or motivation) processes information; because rTMS can produce enduring neuroplastic effects within a target network, the network may be amenable to a therapeutic change in its capacity to autonomously support pathological emotion or motivation. **Targeted indwelling brain stimulation** is a similar although more invasive approach where electrodes are implanted directly within specific brain regions, delivering stronger pulses to a more limited area of a given neural network. This approach is already being used widely for chronic pain conditions (e.g., with peripheral nerve stimulators) and

centrally (e.g., for the treatment of Parkinson's disease), and will likely see greater applications in severe cases of depression, OCD, and addiction.

Deep network therapeutics represents an important frontier of treatment development in addiction psychiatry that aims to optimize the use of novel pharmacological or biophysical tools (e.g., psychoactive neuroplastogens or neuromodulation techniques) to produce especially profound and long-lasting neuroplastic changes in the brain. As a strategy for invoking more profound and enduring recovery trajectories, deep network therapeutics thus incorporates the concepts and goals for integrative and phasic treatments in the following ways:

(1) *Deep network therapeutics aims to change the brain more substantially than what traditional medication treatments are capable of.* Therapeutically changing the brain in a more profound and enduring way to more decisively remit or reduce addiction and mental illness will require changing the architecture and function of whole neural networks and circuits within the brain, rather than just aiming for up- or downregulating single neurotransmitter systems as with traditional psychiatric medications. Various neurostimulatory techniques, implants, or psychoactive neuroplastogen drugs may alter neural network architecture within motivational and limbic circuits in ways that are more profound and enduring than what traditional antidepressants, antipsychotics, or anticraving medications may invoke.

(2) *Deep network therapeutics embraces integrative treatment approaches.* The more profound levels of neuroplastic change that deep network therapeutics aims to invoke involve distributed changes in axodendritic connectivity across neural networks that encompass many neuronal cell types and neurotransmitter systems. Achieving this level of neuroplastic change may require multiple medication or neurostimulatory treatments that converge neuroanatomically and act in concert. Moreover, the appropriate tuning of these neuroplastic changes, corresponding to healthy adaptation of the individual to novel environmental or social conditions, will likely require co-delivery with psychotherapies and/or experiential treatments that help sculpt neural networks in clinically beneficial and recovery-oriented directions.

(3) *Deep network therapeutics will be a form of short-term treatment delivered at specific stages of recovery.* Because the aim of deep network therapeutics is to invoke more profound and enduring changes in neural network

architecture, it will likely be counter-therapeutic to maintain these treatment approaches chronically and without attention to the patient's individualized stages of recovery. Instead, these treatments are likely to be best deployed in the short term and at key phases or transition points in the individual's recovery (e.g., as they transition from one stage or plateau of change into another). As such, deep network therapeutics may produce more efficient and enduring recovery trajectories from PTSD, depressive, manic, or psychotic episodes on the mental health side. In the domain of addiction recovery, more successful transitions between DWT, HR, and FR phases of care and/or transitions between the stages of change) may be accelerated and better sustained by phasic delivery of deep network therapeutics.

Neurostimulatory techniques combined with specific psychotherapies and/or psychoactive neuroplastogens may eventually be used for delimited time durations at specific transition points in recovery trajectories, for example to initiate or consolidate sobriety, or to terminate a co-occurring mental health episode. As delivered in well-supervised and controlled medical settings (e.g., inpatient addiction psychiatry units), these phasic treatments could be used as piggy-back treatments and boosters on top of traditional longer-term psychiatric or addiction medications. A cutting-edge field of psychotherapeutic research that could readily fit into the deep network therapeutics strategy involves the building and use of highly personalized *virtual reality experiences* as artificial (and yet biologically impactful) therapeutic events that could enhance recovery trajectories when combined with neuroplastogens, neurostimulatory techniques, or traditional addiction psychiatry medications.

Conclusion to This Introduction to Addiction Psychiatry

As more physicians, nurses, therapists, and scientists enter the field of addiction psychiatry – which emphasizes the tight interlinkage between mental illness and addiction diseases of the brain – we can expect more effective treatment and better access to treatments for all behavioral health patients. Understanding the bidirectional causal and neurodevelopmental

relationships that exist between addictions and mental illnesses imparts a professional willingness and increased clinical power in treating *both* mental illness and addiction and their various complex comorbid combinations. Addiction psychiatry thus has a unique capability and responsibility across its professional training, clinical, and research missions for advancing integrated dual-diagnosis care. Because dual-diagnosis comorbidities are so highly prevalent and capable of producing such a massive public health burden of expensive-to-treat injuries and body organ diseases, enlarging the field of addiction psychiatry has tremendous potential for decisively reforming and improving the cost-effectiveness of the entire healthcare system. Likewise, the field of addiction psychiatry, if enlarged as a core mission of general psychiatry and equipped with a national infrastructure of interconnected outpatient clinics and inpatient units, has significant potential for powerfully reducing the modern epidemics of homelessness, mass incarceration, overdose, and suicide. In representing the key clinical field for applied motivational neuroscience, addiction psychiatry will also be important to addressing the adverse healthcare and social consequences of internet technologies and artificial intelligence systems. Addiction psychiatry is thus poised to grow with the infusion of new generations of talent that are integrative and multidisciplinary in their interests, rising to the call of solving some of our greatest, most pressing problems in the health and social fabric of modern societies.

BIBLIOGRAPHY

Anthenelli, R. M., N. L. Benowitz, R. West, L. St Aubin, T. McRae, D. Lawrence, J. Ascher, C. Russ, A. Krishen, and A. E. Evins. 2016. Neuropsychiatric safety and efficacy of varenicline, bupropion, and nicotine patch in smokers with and without psychiatric disorders (EAGLES): A double-blind, randomised, placebo-controlled clinical trial. *Lancet*, 387: 2507–20.

Ballester, J., G. Valentine, and M. Sofuoglu. 2017. Pharmacological treatments for methamphetamine addiction: Current status and future directions. *Expert Rev Clin Pharmacol*, 10: 305–14.

Bisaga, A., P. Mannelli, M. Yu, N. Nangia, C. E. Graham, D. A. Tompkins, T. R. Kosten, S. C. Akerman, B. L. Silverman, and M. A. Sullivan. 2018. Outpatient transition to extended-release injectable naltrexone for patients with opioid use disorder: A phase 3 randomized trial. *Drug Alcohol Depend*, 187: 171–78.

Boland, R., M. L. Verduin, P. Ruiz, and A. Shah. 2022. *Kaplan & Sadock's Synopsis of Psychiatry*. Philadelphia, PA: Wolters Kluwer.

Bormann, N. L., and R. A. Chambers. 2023. Esketamine effects on buprenorphine treatment in a comorbid case of opioid addiction, with depression, obsessive-compulsive disorder and chronic pain. *J Pharmacol Clin Toxicol*, 11: 1172.

Brewer, S., M. D. Godley, and L. A. Hulvershorn. 2017. Treating mental health and substance use disorders in adolescents: What is on the menu? *Curr Psychiatry Rep*, 19: 5.

Carroll, K. M., and B. J. Rounsaville. 2007. A perfect platform: Combining contingency management with medications for drug abuse. *Am J Drug Alcohol Abuse*, 33: 343–65.

Chambers, R. A. 2018. *The 2 × 4 Model: A Neuroscience-Based Blueprint for the Modern Integrated Addiction and Mental Health Treatment System*. New York, NY: Routledge.

Chambers, R. A., and C. Toombs. 2021. Deep network pharmacology: Targeting glutamate systems as integrative treatments for jump-starting neural networks and recovery trajectories. *J Psychiatr Brain Sci*, 6: e210008.

Chambers, R. A., and S. C. Wallingford. 2017. On mourning and recovery: Integrating stages of grief and change toward a neuroscience-based model of attachment adaptation in addiction treatment. *Psychodyn Psychiatry*, 45: 451–73.

Chatham-Stephens, K., K. Roguski, Y. Jang, P. Cho, T. C. Jatlaoui, S. Kabbani, E. Glidden, E. N. Ussery, K. F. Trivers, M. E. Evans, B. A. King, D. A. Rose, C. M. Jones, G. Baldwin, L. J. Delaney, P. Briss, M. D. Ritchey, Force Lung Injury Response Epidemiology/Surveillance Task, and Force Lung Injury Response Clinical Task. 2019. Characteristics of hospitalized and nonhospitalized patients in a nationwide outbreak of e-cigarette, or vaping, product use-associated lung injury – United States, November 2019. *MMWR Morb Mortal Wkly Rep*, 68: 1076–80.

Crum, R. M., J. C. Anthony, S. S. Bassett, and M. F. Folstein. 1993. Population-based norms for the Mini-Mental State Examination by age and educational level. *JAMA*, 269: 2386–91.

Culbertson, C. S., J. Bramen, M. S. Cohen, E. D. London, R. E. Olmstead, J. J. Gan, M. R. Costello, S. Shulenberger, M. A. Mandelkern, and A. L. Brody. 2011. Effect of bupropion treatment on brain activation induced by cigarette-related cues in smokers. *Arch Gen Psychiatry*, 68: 505–15.

Drake, R. E., K. T. Mueser, M. F. Brunette, and G. J. McHugo. 2004. A review of treatments for people with severe mental illnesses and co-occurring substance use disorders. *Psychiatr Rehabil J*, 27: 360–74.

Felitti, V. J., R. F. Anda, D. Nordenberg, D. F. Williamson, A. M. Spitz, V. Edwards, M. P. Koss, and J. S. Marks. 1998. Relationship of childhood abuse and

household dysfunction to many of the leading causes of death in adults. *Am J Prev Med*, 14: 245–58.

Galanter, M. 1993. Network therapy for addiction: A model for office practice. *Am J Psychiatry*, 150: 28–36.

Galanter, M., H. D. Kleber, and K. T. Brady (eds.). 2014. *Textbook of Substance Abuse Treatment*. Washington, DC: American Psychiatric Publishing.

Hackman, D. T., M. S. Greene, T. J. Fernandes, A. M. Brown, E. R. Wright, and R. A. Chambers. 2014. Prescription drug monitoring program inquiry in psychiatric assessment: Detection of high rates of opioid prescribing to a dual diagnosis population. *J Clin Psychiatry*, 75: 750–56.

Herrold, A. A., S. L. Kletzel, B. C. Harton, R. A. Chambers, N. Jordan, and T. L. Pape. 2014. Transcranial magnetic stimulation: Potential treatment for co-occurring alcohol, traumatic brain injury and posttraumatic stress disorders. *Neural Regen Res*, 9: 1712–30.

Hoffman, K. T., R. S. Marvin, G. Cooper, and B. Powell. 2006. Changing toddlers' and preschoolers' attachment classifications: The Circle of Security intervention. *J Consult Clin Psychol*, 74: 1017–26.

Jonas, D. E., H. R. Amick, C. Feltner, G. Bobashev, K. Thomas, R. Wines, M. M. Kim, E. Shanahan, C. E. Gass, C. J. Rowe, and J. C. Garbutt. 2014. Pharmacotherapy for adults with alcohol use disorders in outpatient settings: A systematic review and meta-analysis. *JAMA*, 311: 1889–900.

Kalapatapu, R. K., and R. A. Chambers. 2009. Novel objective biomarkers of alcohol use: Potential diagnostic and treatment management tools in dual diagnosis care. *J Dual Diagn*, 5: 57–82.

Kaskutas, L. A. 2009. Alcoholics anonymous effectiveness: Faith meets science. *J Addict Dis*, 28: 145–57.

Kilaru, A. S., A. Xiong, M. Lowenstein, Z. F. Meisel, J. Perrone, U. Khatri, N. Mitra, and M. K. Delgado. 2020. Incidence of treatment for opioid use disorder following nonfatal overdose in commercially insured patients. *JAMA Netw Open*, 3: e205852.

Kosten, T. R., and P. G. O'Connor. 2003. Management of drug and alcohol withdrawal. *N Engl J Med*, 348: 1786–95.

Kreek, M. J., K. S. LaForge, and E. Butelman. 2002. Pharmacotherapy of addictions. *Nat Rev Drug Discov*, 1: 710–26.

Kristenson, H. 1995. How to get the best out of Antabuse. *Alcohol Alcohol*, 30: 775–83.

Krystal, J. H. 2007. Neuroplasticity as a target for the pharmacotherapy of psychiatric disorders: New opportunities for synergy with psychotherapy. *Biol Psychiatry*, 62: 833–34.

Mangrum, L. F., R. T. Spence, and M. Lopez. 2006. Integrated versus parallel treatment of co-occurring psychiatric and substance use disorders. *J Subst Abuse Treat*, 30: 79–84.

Mattick, R. P., C. Breen, J. Kimber, and M. Davoli. 2009. Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. *Cochrane Database Syst Rev*, 2009: CD002209.

McLellan, A. T., D. C. Lewis, C. P. O'Brien, and H. D. Kleber. 2000. Drug dependence, a chronic medical illness: Implications for treatment, insurance, and outcomes evaluation. *JAMA*, 284: 1689–95.

Mendola, A., and R. L. Gibson. 2016. Addiction, 12-step programs, and evidentiary standards for ethically and clinically sound treatment recommendations: What should clinicians do? *AMA J Ethics*, 18: 646–55.

Miller, W. R., and S. Rollnick. 2002. *Motivational Interviewing: Preparing People for Change*. New York, NY: Guilford.

Minkoff, K. 2001. Best practices: Developing standards of care for individuals with co-occurring psychiatric and substance use disorders. *Psychiatr Serv*, 52: 597–99.

Minkoff, K. 1991. Dual diagnosis: Counseling the mentally-ill substance-abuser. *J Stud Alcohol*, 52: 505–05.

Minkoff, K., and C. A. Cline. 2004. Changing the world: The design and implementation of comprehensive continuous integrated systems of care for individuals with co-occurring disorders. *Psychiatr Clin North Am*, 27: 727–43.

Moeller, K. E., K. C. Lee, and J. C. Kissack. 2008. Urine drug screening: Practical guide for clinicians. *Mayo Clin Proc*, 83: 66–76.

Molyneux, A. 2004. Nicotine replacement therapy. *BMJ*, 328: 454–56.

Moos, R. H. 2007. Theory-based active ingredients of effective treatments for substance use disorders. *Drug Alcohol Depend*, 88: 109–21.

Mueser, K. T., R. E. Drake, S. Sigmon, and M. F. Brunetter. 2005. Psychosocial interventions for adults with severe mental illnesses and co-occurring substance use disorders: A review of specific interventions. *J Dual Diagn*, 1: 57–82.

Mueser, K. T., D. L. Noordsky, R. E. Drake, and L. B. Fox. 2003. *Integrated Treatment for Dual Disorders: A Guide to Effective Practice*. New York, NY: Guilford Press.

Najavits, L. M. 2003. Seeking safety: A new psychotherapy for posttraumatic stress disorder and substance use disorder. In P. Ouimette and P. J. Brown (eds.), *Trauma and Substance Abuse: Causes, Consequences, and Treatment of Comorbid Disorders*. Washington, DC: American Psychological Association.

Potenza, M. N., M. Sofuoglu, K. M. Carroll, and B. J. Rounsaville. 2011. Neuroscience of behavioral and pharmacological treatments for addictions. *Neuron*, 69: 695–712.

Prochaska, J. O., and C. C. DiClemente. 2005. The transtheoretical approach. In J. C. Norcross and M. R. Goldfried (eds.), *Handbook of Psychotherapy Integration*. New York, NY: Oxford University Press.

Renner, J. A., Jr. 2004. How to train residents to identify and treat dual diagnosis patients. *Biol Psychiatry*, 56: 810–16.

Rounsaville, B. J., N. M. Petry, and K. M. Carroll. 2003. Single versus multiple drug focus in substance abuse clinical trials research. *Drug Alcohol Depend*, 70: 117–25.

Sajid, A., A. Whiteman, R. L. Bell, M. S. Greene, E. A. Engleman, and R. A. Chambers. 2016. Prescription drug monitoring program data tracking of opioid addiction treatment outcomes in integrated dual diagnosis care involving injectable naltrexone. *Am J Addict*, 25: 557–64.

SAMSHA. 2009. *Integrated Treatment for Co-occurring Disorders: The Evidence*. Rockville, MD: U.S. Department of Health and Human Services.

Saxon, A. J., Y. I. Hser, G. Woody, and W. Ling. 2013. Medication-assisted treatment for opioid addiction: Methadone and buprenorphine. *J Food Drug Anal*, 21: S69–S72.

Shen, Y. I., A. J. Nelson, and B. G. Oberlin. 2022. Virtual reality intervention effects on future self-continuity and delayed reward preference in substance use disorder recovery: Pilot study results. *Discov Ment Health*, 2: 19.

Sullivan, J. T., K. Sykora, J. Schneiderman, C. A. Naranjo, and E. M. Sellers. 1989. Assessment of alcohol withdrawal: The revised clinical institute withdrawal assessment for alcohol scale (CIWA-Ar). *Br J Addict*, 84: 1353–57.

Wesson, D. R., and W. Ling. 2003. The Clinical Opiate Withdrawal Scale (COWS). *J Psychoactive Drugs*, 35: 253–59.

White, W. L. 2014. *Slaying the Dragon: The History of Addiction Treatment and Recovery in America*. Bloomington, IL: Chestnut Health Systems/Lighthouse Institute.

Williams, A. R., H. Samples, S. Crystal, and M. Olfson. 2020. Acute care, prescription opioid use, and overdose following discontinuation of long-term buprenorphine treatment for opioid use disorder. *Am J Psychiatry*, 177: 117–24.

Williams, J., M. Steinberg, M. H. Zimmerman, and E. Salsberg. 2009. Training psychiatrists and advanced practice nurses to treat tobacco dependence. *J Am Psychiatr Nurses Assoc*, 15: 50–58.

Yonkers, K. A., A. Forray, H. B. Howell, N. Gotman, T. Kershaw, B. J. Rounsaville, and K. M. Carroll. 2012. Motivational enhancement therapy coupled with cognitive behavioral therapy versus brief advice: A randomized trial for treatment of hazardous substance use in pregnancy and after delivery. *Gen Hosp Psychiatry*, 34: 439–49.

Ziedonis, D. M. 2004. Integrated treatment of co-occurring mental illness and addiction: Clinical intervention, program, and system perspectives. *CNS Spectr*, 9: 892–904.

Index