Current Clinical Psychiatry
Series Editor: Jerrold F. Rosenbaum

John F. Kelly
Sarah E. Wakeman *Editors*

Treating Opioid Addiction

Humana Press

Current Clinical Psychiatry

Series Editor

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Current Clinical Psychiatry offers concise, practical resources for clinical psychiatrists and other practitioners interested in mental health. Covering the full range of psychiatric disorders commonly presented in the clinical setting, the Current Clinical Psychiatry series encompasses such topics as cognitive behavioral therapy, anxiety disorders, psychotherapy, ratings and assessment scales, mental health in special populations, psychiatric uses of nonpsychiatric drugs, and others. Series editor Jerrold F. Rosenbaum, MD, is Chief of Psychiatry, Massachusetts General Hospital, and Stanley Cobb Professor of Psychiatry, Harvard Medical School.

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Foreword

There's a campfire story about a worm who complains to Mother Nature about being ugly. Mother Nature shows him two magical goblets, one filled with everything good and the other filled with everything bad. The worm wants to drink from the goblet of good things, but Mother Nature tells him that such an easy choice is not given to living things. Rather, the worm must drink from a channel connecting the two goblets in which the contents of each are mixed.

Upon doing so, the worm is horrified to see that he is uglier than ever. But later, he falls asleep and wakes up in a cocoon, from which he emerges as a beautiful butterfly.

I think about this story often in relation to drugs, particularly Mother Nature's warning that living things are fated to drink from the channel in which good and bad are invariably mixed. Opioids illustrate the point. People unfortunate enough to live in countries without them often die agonizing deaths from cancer and experience excruciating pain after injuries. Throughout the world, they are essential to the practice of medicine. All of that resides in the goblet of good things.

But the other goblet holds contents of a disturbingly different character. Opioids are quite addictive and when taken long term can cause significant adverse side effects and enduring health problems [1]. The most feared of these effects is overdose, which stems from the respiratory depression caused by this potent class of drugs. About 50,000 people died of opioid overdose in the United States in 2016 alone [2, 3], and that number will climb in the years ahead. Further, for every fatality there are about 30 nonfatal overdoses in which the brain and other organs may be damaged permanently by anoxia [4].

The opioid crisis in the United States and Canada is insoluble without returning opioid prescribing to the sane levels seen in other developed countries. This will require confronting deep-pocketed, politically powerful interests, but will also save and improve countless lives by reducing the future incidence of opioid addiction. Yet this noble preventive work will do nothing for those individuals for whom it comes too late, namely, those who are already addicted.

It is for such unfortunate individuals that this fine book was written. If anything uplifting can be said about opioid addiction, it is that there are more effective interventions available for those who suffer from it than for addiction to many other drugs (e.g., methamphetamine, cocaine, benzodiazepines). As the chapters to follow skillfully explicate, these include resources whose purposes range from keeping

opioid-addicted individuals alive (e.g., naloxone), to stabilizing them physiologically so that they can function through the day, desist from crime, and participate in other services (e.g., methadone), to resolving the co-occurring problems that are prevalent among opioid-addicted people (e.g., psychological counseling, antivirals for Hepatitis C, legal advice, job training), to helping them build a full and gratifying life in recovery (e.g., mutual help and recovering community organizations).

All of these technologies – undergirded by a responsive, comprehensive, equitable, health care provision and insurance system – are essential for helping the population of people experiencing opioid addiction. But an additional, equally essential, thread running more implicitly through this volume should not be missed: a moral commitment to treating addicted individuals as human beings worthy of respect, caring, and compassion. Only by combining the best impulses of our hearts and the best output of our scientific minds can we adequately support the recovery of the millions of Americans whose lives are blighted by opioid addiction.

Keith Humphreys
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Preface

The last several hundred years of human history has seen millions killed by epidemics mostly related to infectious diseases. Whether by smallpox, tuberculosis, polio, malaria, cholera, typhus, influenza, or HIV/AIDS, hundreds of millions have suffered debilitating illness and lost their lives. In the modern era of the past 100 years, especially in middle- and high-income countries globally, we have moved away largely from the threat of infectious disease as the big killer and succumbed to diseases related – in the vast majority of cases – to cigarette smoking, alcohol, other drug use, and diseases caused by overeating, poor diet, and sedentariness. As physician Thomas Trotter noted in his well-known book, *An Essay, Medical, Philosophical and Chemical, on Drunkenness and Its Effects on the Human Body* (1804): "Mankind, ever in pursuit of pleasure, have reluctantly admitted into the catalogue of their diseases, those evils which were the immediate offspring of their luxuries." Trotter was alluding to alcohol addiction, which he described as a "disease of the mind."

The notion of "reluctant admission," which he points out so eloquently in his stated observation, is all too poignant a concept in the current era. His notion of addiction being a "disease of the mind" also foreshadowed our current neuroscientific understanding of addiction. The human brain is wired to produce subjective experiences of pleasure and reward in response to food, social bonding, and sex. These natural reinforcers are powerfully remembered and, throughout human evolution, have provided the motivation for survival and reproduction. In more recent centuries beginning with distillation – in the case of alcohol – followed by an advancing industrial pharmacy that synthesized and enhanced the potency of other chemical compounds, the ability to induce abnormally high levels of reward that outcompete natural rewards has accelerated and become commonplace. The gin epidemic of the 1700s through opium epidemics of the 1800s, to cocaine/crack cocaine in the 1980s, crystal methamphetamine of the 1990s and 2000s, to a current devastating opioid addiction and overdose epidemic, concentrated psychoactive substances have demonstrated their ability to overpower the brain's natural reward neurocircuitry, which can lead to addictive disease and, frequently, premature death.

The reasons for such epidemics are fueled and shaped by many forces. In the case of the current US opioid epidemic, sociocultural, economic, and political factors have permitted or actively facilitated widespread dissemination of pharmaceutical opioids intended to alleviate pain and suffering. Beginning with the flood of

prescribed, ostensibly "non-addicting," but ultimately highly seductive, pain killing opioids, through influxes of illicit cheap heroin, followed by even more powerful fentanyl analogs, these sociocultural and economic factors seduced a nation into a lethal trap.

This book is intended to help us get out of this trap and address the current crisis through an up-to-date and thorough examination of the etiology of the current opioid epidemic, its epidemiology, and the policies, and treatment and recovery approaches, forged and applied to successfully address it. Our hope is that this text will educate, inform, and empower students, clinicians, administrators, researchers, and policy makers, to understand the origin, nature, and scope of the current opioid crisis and how to effectively address and resolve it.

We are grateful for the help of Connie Walsh and Nadina Persaud at Springer Publishing for their expert help and for shepherding the book along to completion. We would also like to thank Alexandra Abry for her help in keeping things so expertly organized and for helping to facilitate communications among the editorial team and the chapter contributors. We are grateful also to the series editor, Dr. Jerrold Rosenbaum, MD, Chief of Psychiatry at the Massachusetts General Hospital and The Stanley Cobb Professor of Psychiatry at Harvard Medical School, for his suggestion to tackle this topic and produce a text tackling the current opioid crisis as the latest edition in his clinical series.

As always, as editors we have had the privilege of receiving an education from so many expert authors contained herein who have contributed a wealth of knowledge on a topic of supreme and urgent clinical and public health importance. It is our sincere hope that this volume will help outline the causes, consequences, clinical course, and successful resolution strategies that will ultimately bring the current crisis to an end and very importantly, outline the powerful lessons learned from the hundreds of thousands of deaths that will ultimately prevent this from ever happening again.

Boston, MA, USA — John F. Kelly
Charlestown, MA, USA — Sarah E. Wakeman

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Killing More than Pain: Etiology and Remedy for an Opioid Crisis

1

John F. Kelly and Sarah E. Wakeman

Abbreviations

CBT	Cognitive-behavioral therapy
CDC	Centers for Disease Control and Prevention
EVD	Ebola virus disease
FDA	Food and Drug Administration
JCAHO	The Joint Commission on Accreditation of Healthcare Organizations
MI	Motivational interviewing
NA	Narcotics Anonymous
OUD	Opioid use disorder
PMPs	Prescription monitoring programs
SARS	Severe acute respiratory syndrome
TSF	Twelve-step facilitation

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Introduction

The search for effective pain relief has been ever present across human history. The discovery of opium's ability to relieve pain stimulated the refinement of opium and generation of synthetic analogues to create more effective, potent, and faster acting analgesics. The social and economic value of opioid analgesics has remained high not only due to their demonstrated efficiency in mitigating pain but also their noteworthy ability to reliably produce pleasant rewarding psychological side effects. Consequently, at various times during the past several hundred years, opioid drugs have sparked wars, fueled black markets, driven up violence and cartel crime, and triggered numerous opioid addiction and overdose death epidemics around the world.

The therapeutic and humane desire to address pain—one of the most debilitating and disturbing of all human experiences—together with enhanced pharmaceutical discoveries in medication design, manufacture, marketing, sales, and distribution of oral opioid analgesic medications has led more recently to excess availability and accessibility. The additional seductive pharmacological nature of these potent compounds, and the ability to administer doses directly into the bloodstream via hypodermic needles, producing intense euphoria, sedation, and hypnosis (sleep), can lead to some developing compulsive use and addiction. As societies have grappled with rising rates of use and addiction, some have reflexively reached for supply-centric policies to reduce access. While supply reduction is a major piece of the puzzle, without addressing the demand side of the equation, these approaches can have the inadvertent effect of shifting people who were using prescription opioids to the often cheaper, more readily available, but more lethal, options of heroin and illicitly manufactured fentanyl.

In countries such as the United States, between approximately the late 1990s and 2018, rates of population opioid exposure and opioid overdose deaths have risen sharply and steadily creating one of the largest overdose death epidemics in modern history—possibly ever. How we got here, what we can do about it, and how we can prevent it in the future, are the fundamental questions that we attempt to answer in this chapter. To begin, below we describe briefly the nature, structure, origin, and growth in the use of opioid analgesics and subsequently describe the etiology and epidemiology of the current crisis using broad public health and health belief models as frameworks to help guide understanding. In the second section, we describe the approaches that have been applied to address both supply (e.g., overprescribing) and demand (e.g., overdose intervention, pharmacological and psychosocial treatments) sides of the equation. In the final section, we review the lessons learned in an attempt to outline strategies to prevent future epidemics.

Context: Origin and Growth in the Use of Opioids

Poppies, Pain, and Panacea

A large variety of natural, semisynthetic, and fully synthetic opioid-based medications have become increasingly available as the extraction, synthesis, and

manufacturing processes of opioids have become more efficient and refined. The opium poppy, from which the morphine molecule comes, is a naturally occurring flowering plant found in many parts of the world and cultivated explicitly in China and parts of the Middle East for its pain killing and euphoria-inducing properties for both licit and illicit markets. Opium is the dried aqueous gum that can be leached from the opium poppy, about 12% of which is the alkaloid analgesic, morphine. Morphine can be extracted, and a more potent formulation can be derived (diacetylmorphine or heroin), which is used as a strong analgesic to address severe pain as well as used recreationally to induce rapid and intense euphoria.

The discovery and use of morphine from the opium poppy is recorded dating back to ancient Egypt. Morphine and its derivatives (codeine) can also be used effectively to treat a range of other common ailments including severe cough and diarrhea, but opioids' refinement and widespread synthetic analogue manufacture (e.g., fentanyl) is a product of modern biochemistry and the pharmaceutical industry.

Pharmacodynamically, opioids are broken down upon entering the body and bind to the mu-opioid receptor producing analgesia, euphoria, and anxiety-reducing effects. In high enough doses, however, these compounds can produce respiratory depression and death. When mixed with other sedative-hypnotic drugs, such as alcohol or benzodiazepines, respiratory depression is exacerbated and the risk of fatal overdose increases. Research suggests that for each additional illicit drug administered in combination with an opioid, the risk of death from opioids doubles [1], and, in fact, many fatal overdoses are caused in this synergistic fashion.

Killing More Than Pain: The Double-Edged Sword of Opioids

The discovery of the pain-killing potential of opium-based tinctures and, later, more potent pharmaceutically enhanced analogues has been both an immense blessing and at the same time a worrisome curse—"too much of a good thing" can create problems. The degree of use of pharmaceuticals, like many other commodities, is socially, economically, politically, and culturally based. The United States is among the largest global consumers of opioids, with prescribing rates that outpace many peer nations; however, while consumption of opioids in the United States is undoubtedly high, it has been overstated. For example, while it is commonly reported that the United States consumes "80% of the world's supply of opioids," it is because within that figure are certain opioid medications that are exclusively marketed in the United States while other countries use similar, but slightly different, opioid compounds. Consequently, a more accurate estimate is that while the United States has approximately 4.4% of the world's population, it consumes about 30% of the world's global supply of opioids [2]. Still, as shown in Fig. 1.1, using standard daily doses per million inhabitants, relative to other middle- and high-income countries, opioid use is disproportionately high but not as high as is commonly stated. Perhaps the interplay of a strong biotech industry, capitalist consumer-oriented free market economy, and constitutionally based cultural expectations that explicitly endorse the right to "the pursuit of happiness" has promoted America's demand for rapid pharmaceutical remedies for pain and suffering. Within such an economic and

sociocultural context, however, like many industrialized countries, the United States has sought to institute safeguards to curb the potential appetite for "too much of a good thing." For example, it possesses among the strongest protections and regulations worldwide regarding quality and safety of medications, and administrative oversight regarding scheduling, prescribing, and marketing (e.g., the Food and Drug Administration [FDA]; Prescription Monitoring Programs [PMPs]). As explained below, a number of forces converged to create the current overdose epidemic and opioid addiction crisis seen that has emerged since the late 1990s.

Conceptual Models for Understanding Drug Epidemics

It can be helpful to draw upon well-developed conceptual frameworks for helping to understand, and thus intervene upon, different disease epidemics that occur from time to time. The public health model of disease suggests there are three major factors that interact to influence the spread of an epidemic: the agent (e.g., the presence of an environmental toxin; in this case, opioids), the host (i.e., the human beings exposed to the opioid), and the environment (e.g., the variables that can influence the degree to which the host is exposed to the opioid; see Fig. 1.1). To the extent that an agent (e.g., opioid) can cause harm to a host (person), the environment can play a crucial role in mitigating or exacerbating that harm. In the case of addiction or substance use disorder, more generally, this public health model of disease is complicated slightly further, because—as is the case with opioids—the agent is highly desired by the host since it can kill pain as well as produce intense pleasure. All other things being equal, if it becomes widely available, easily accessible, affordable, legal, and medically prescribed—and thus has lower stigma attached to it—its use will increase. Given that opioids are known to cause

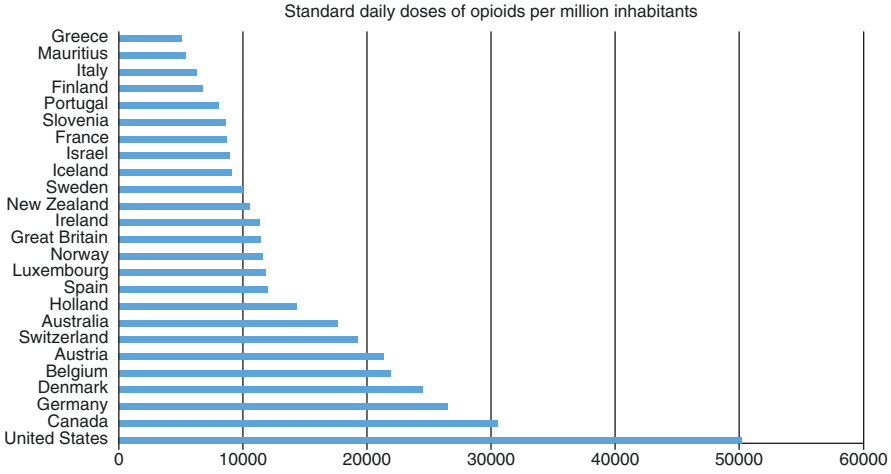

Fig. 1.1 Standard daily doses of opioids per million inhabitants across developed nations [2]

addiction and increase risk for overdose death and are heavily regulated for safety and quality, how could these potent and seductive medications become so widely available and easily accessible?

It seems likely that two major factors influenced this high degree of prescription use of opioids and population exposure. One was the perception that these medications are very safe and hardly ever led to addiction among pain patients. Strikingly, based upon a single, one-paragraph publication in 1980 [3]—albeit one that was published in perhaps the most highly influential medical journal of all (the *New England Journal of Medicine*)—that was heavily promoted and cited, it was widely believed that addiction was almost nonexistent among medical patients treated in hospital settings with opioid analgesics such as hydrocodone and hydromorphone. Given the journal's medical prestige, this publication and its common citation were rarely questioned and became widely referred to with little scrutiny. The pharmaceutical industry was only too happy to take advantage of what appeared to be a scientific medical blessing on the liberal use of their opioid analgesics from which they stood to profit.

A perceived strong scientific and medical sanction regarding safety and efficacy opened the door to advertising to physicians as well as directly to consumers. The Health Belief Model [4] suggests that people are likely to take a health-related behavioral preventative action if they perceive that the action will decrease the chances of a particular personal negative health outcome. If people believe that the threat is low or practically nonexistent, or not severe, then they are unlikely to engage in such a preventive action. In this case, consumers were led to believe that there was no threat and encouraged to take such medications by health-care providers—culturally, highly trusted entities, who similarly believed these medications had very low risk for harm.

At the same time in the United States, there was a push from several organizations to address pain much more aggressively and there was widespread belief that pain was being inadequately assessed and poorly treated in medical settings. Unrelieved pain was considered to be a major, yet completely avoidable, public health problem. In 1997, a collaborative project was initiated to integrate pain assessment and management into clinical best practice standards. Furthermore, in 2001, all patient care organizations accredited by the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) were required to document proper management of pain, and pain became the "fifth vital sign"—as integral to standard basic medical "best practice" assessment as obtaining a patient's body temperature or blood pressure reading. Adding to this is the fact that prescription opioids were purported and perceived to be "safe" and "nonaddicting," and there was a perfect storm brewing which since then has created hundreds of thousands of casualties.

It was not just the number of prescriptions that went up exponentially during the 1990s and 2000s but also the *amount* of opioid pills allotted per prescription. Often dozens of potent opioid pills were prescribed for fairly minor to moderate and short-lived, acute pain (e.g., tooth extraction, minor surgery), such that only a fraction of the prescribed pills were needed creating an accumulating glut of residual unused prescription opioids, unwittingly increasing availability and potential accessibility in the community.

For any desirable commodity, availability, accessibility, and price are major factors influencing a product's consumption. Other things being equal, the more available, accessible, and cheaper a desirable product is, the greater is its consumption. When asked in national surveys conducted in the United States from where individuals had obtained their (prescription) opioids, 54% reported that they obtained them from a friend or relative from a medicine cabinet at home or from a friend or relative who obtained them from their own medicine cabinet [5]. While direct prescription to individual pain patients puts some at risk of developing addiction, likely to be an even larger issue was how these excess pills flooded the community, increasing access and nonmedical use.

Combining the conceptual frameworks of the public health model and the Health Belief Model, Americans ("host") perceived a decrease in risk and an increase in perceived safety, while opioids ("agent") became more available and accessible, and the cultural, political, and social environment was such that it was completely legal and medically sanctioned to be using these powerful medications without concern (Fig. 1.2). Price too was relatively low in the early years of the epidemic, because for the most part prescribed opioids were covered by insurance, or otherwise cheap. This fact tended also to bias in favor of White American consumers who more likely had health insurance, who were potentially more likely to be prescribed due to unconscious racial bias among physicians, and who, in contrast to prior opioid epidemics, became overrepresented among those overdosing on opioids. Compared to prior mostly male, urban-based, heroin epidemics of the 1960s where the average age of onset was around 16 years old, individuals misusing opioids between 2000 and 2014 were older (mean age, 22.9 years) men and women living in less urban areas who were introduced to opioids through prescription drugs (75.0%). Also, Whites and non-Whites were equally represented in those initiating use prior to the 1980s, but nearly 90% of those who began use between 2000 and 2014 were White [6]. In more recent years, however, Blacks and Hispanic and Latino Americans have shown steady increases in overdose deaths, and overdose deaths among Black Americans in particular have risen more sharply since 2014 accounted for largely by an increase in overdoses among older Black men (Fig. 1.3. CDC, 2018).

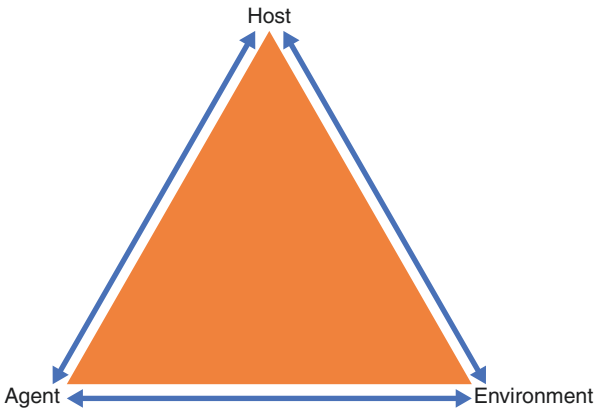

Fig. 1.2 Public health model framework for understanding drug epidemics

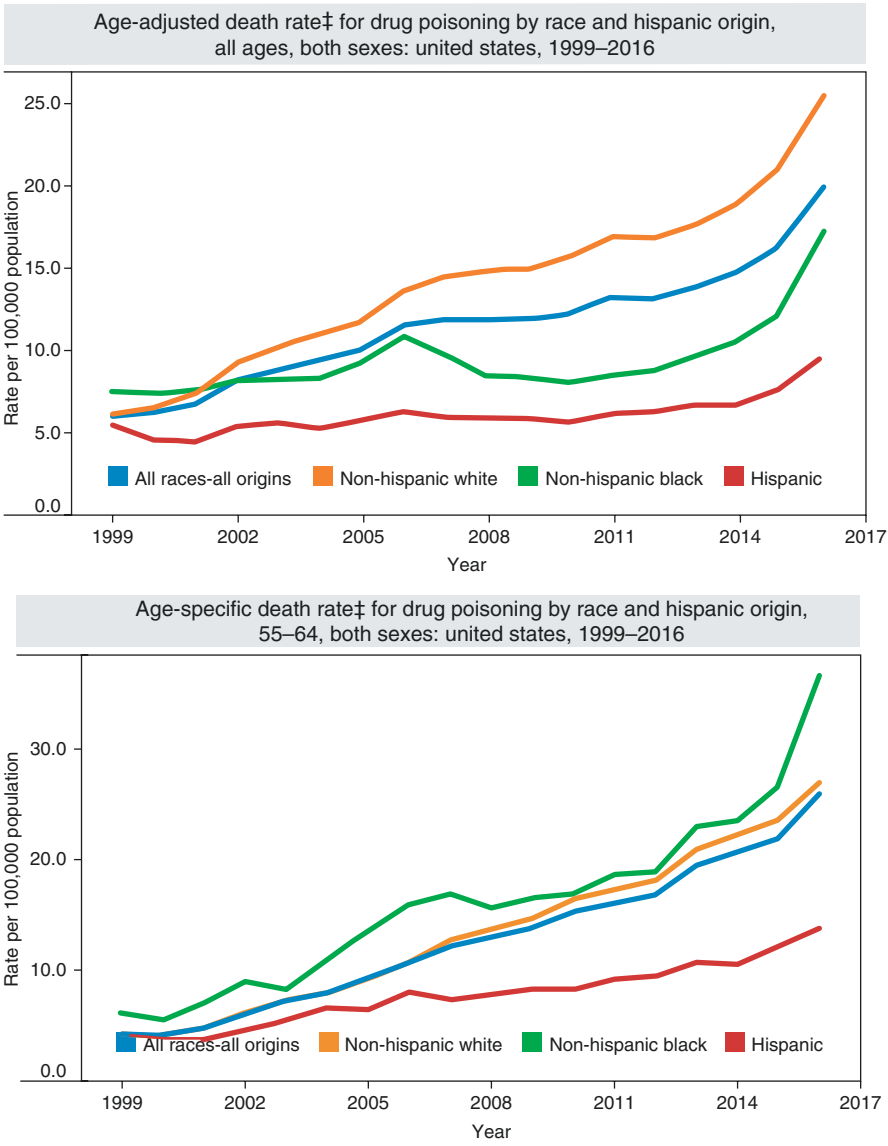

Fig. 1.3 Changes in opioid overdose death rates by racial-ethnic groups. (From CDC. Centers of Disease Control. Drug Poisoning Mortality in the United States, 1999–2016. Accessed at: https://www.cdc.gov/nchs/data-visualization/drug-poisoning-mortality/)

Epidemiology of Opioid Misuse, Opioid Use Disorder, and Overdose Deaths

For the reasons outlined above, between 1999 and 2016 there has been a large increase in the numbers of people misusing prescription opioids in the United States,

in those meeting criteria for an opioid use disorder, and in overdose deaths. Strikingly, overdose is now the leading cause of death for people under the age of 50 in the United States [7]. From 1999 to 2016, for example, more than 630,000 people have died from a drug overdose and it estimated that approximately two-thirds of these involved opioids specifically.

According to the US Centers for Disease Control and Prevention (CDC), in 2016, the number of overdose deaths involving opioids (including prescription opioids and illegal opioids like heroin and illicitly manufactured fentanyl) was five times higher than that in 1999 [8]. Currently, on average, 115 Americans die every day from an opioid overdose. In 2016, approximately 42,000 of the more than 64,000 individuals who died from an overdose died from an opioid overdose (Fig. 1.4). In addition, 11.5 million Americans misused prescription opioids and 2.1 million met criteria for an opioid use disorder in 2016. These rates may underestimate the true prevalence of opioid use disorder as they are based on household data which excludes institutionalized, homeless, or incarcerated individuals. A recent study in Massachusetts found the prevalence of opioid use disorder to be 4.6% [9].

In the current opioid crisis that has resulted in so many opioid overdose deaths, there have been three broad waves (Fig. 1.5). The first large increase began in 1999 with a steady linear rise in deaths from prescription opioids. This was followed by a second wave of heroin-related overdose deaths beginning in 2010, followed by a third wave in synthetic overdose deaths beginning in 2013. Opioid misuse and opioid use disorders are more common among men than women, but both have experienced increasing overdose death rates at roughly the same increased rate since 1999.

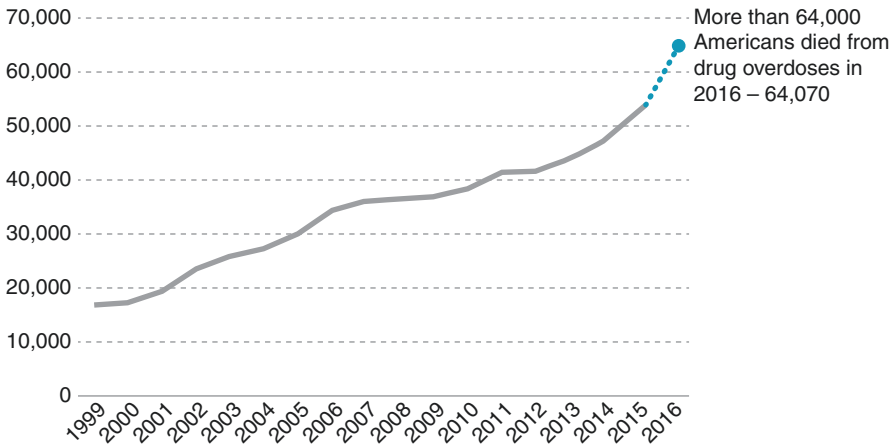

Fig. 1.4 Increasing trend in US overdose deaths 1999–2016. Total US drug deaths. (Source: CDC WONDER. Accessed at: https://wonder.cdc.gov/)

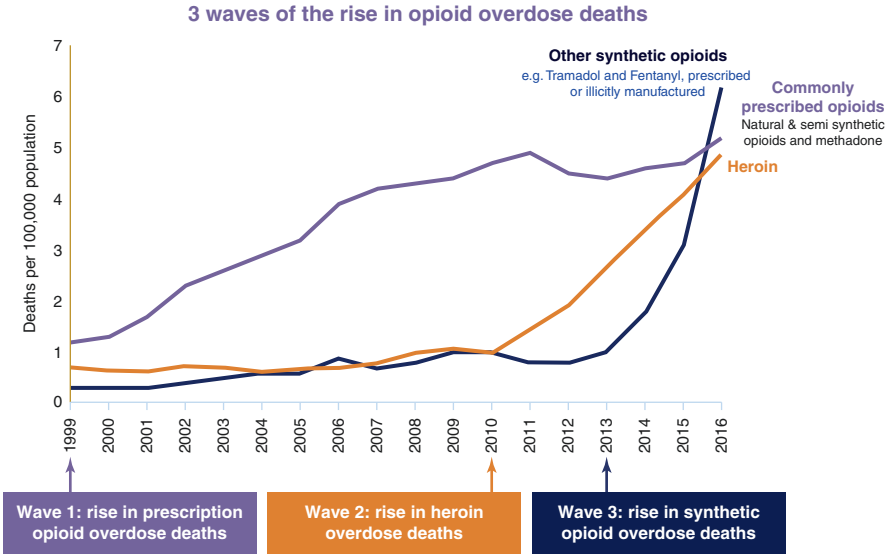

Fig. 1.5 Trends in opioid overdose death rates in relation to prescription opioids, heroin, and synthetic opioids (e.g., fentanyl). (Source: CDC 2018 https://www.cdc.gov/drugoverdose/epidemic/index.html - Response to the Crisis: Reducing Supply, Increasing Prevention, Treatment and Recovery Supports. National Vital Statistics System Mortality File)

Addressing Opioid Misuse, Disorders, and Overdose Deaths

Considering the public health model once again of agent (opioids), host (people), and environment, there have been increasing concerted attempts to reduce the supply of opioids (the agent) into the environment through prescriber education, prescribing limits, and prescription monitoring program initiatives. There have also been large-scale efforts to protect the host from fatal overdose through education and prevention efforts, as well as emergency intervention efforts (e.g., with widespread distribution of intranasal naloxone [Narcan]) and increased access to medications, psychosocial interventions, and harm reduction strategies (safe injection facilities and syringe service programs). From a policy standpoint, the latter are collectively known as "demand reduction" efforts in the supply and demand equation as they are designed to reduce the appeal of, and desire for, opioids through treating opioid use disorders.

Reducing Supply and Accessibility to Opioids

As noted, given that availability and accessibility are two major contributors to increased consumption of opioids, there has been a major concerted effort to change prescribing practices through education, monitoring, and restrictions, as well as "take

back" programs designed to reduce exposures in the general population. States and insurers have begun passing legislation and implementing policies aimed at curtailing access to prescription opioids. While responsible and cautious prescribing of opioids is critically important to reduce unnecessary exposure and access for opioid-naïve individuals to reduce the incidence of opioid use and use disorder, supply-focused strategies are unlikely to benefit people who are already using opioids, including those with opioid use disorder or chronic pain. Prescribing guidelines, such as the 2016 CDC guidelines [10], offered approaches for more judicious use of opioids limiting exposure to opioids in acute pain, continuously addressing the risk and benefit of opioid treatment, and screening and offering treatment for opioid use disorder. At the same time, these guidelines recognized the complexity of managing individuals who were started on high doses of opioids previously and the importance of safeguarding against patient abandonment in these scenarios in the case of opioid use disorder (Fig. 1.6).

CDC recommendations for prescribing opioids for chronic pain outside of active cancer, palliative, and end-of-life care.

Determining When to Initiate or Continue Opioids for Chronic Pain

1. Nonpharamacologic therapy and nonopioid pharmacologic therapy are preferred for chronic pain. Clinicians should consider opioid therapy only if expected benefit for both pain and function are anticipated to outweight risks to the patient. If opioids are use, they should be combined with nonpharmacologic therapy and nonopioid pharmacologic therapy, as appropriate.
2. Before starting opioid therapy for chronic pain, clinicians should establish treatment goals with all patients, including realistic goals for pain and function, and should consider how therapy will be discontinued if benefits do not outweigh risks. Clinicians should continue opioid therapy only if there is clinically meaningful improvement in pain and function that outweighs risks to patient safety.
3. Before starting and periodically during opioid therapy, clinicians should discuss with patients known risks and realistic benefits of opioid therapy and patient and clinician responsibilities for managing therapy.

Opioid Selection, Dosage, Duration, Follow-Up, and Discontinuation

4. When starting opioid therapy for chronic pain, clinicians should prescribe immediate-release opioids instead of extended-release/long-acting (ER/LA) opioids.
5. When opioids are started, clinicians should prescribe the lowest effective dosage. Clinicians should use caution when prescribing opioids at any dosage, should carefully reassess evidence of individual benefits and risks when increasing dosage to ≥50 morphine milligram equivalents (MME)/day, and should avoid increasing dosage to ≥90 MME/day or carefully justify a decision to titrate dosage to ≥90 MME/day
6. Long-term opioid use often begins with treatment of acute pain. When opioids are used for acute pain, clinicians should prescribe the lowest effective dose of immediate-release opioids and should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids. Three days or less will often be sufficient; more than seven days will rarely be needed.
7. Clinicians should evaluate benefits and harms with patients within 1 to 4 weeks of starting opioid therapy for chronic pain or of dose escalation. Clinicians should evaluate benefits and harms of continued therapy with patients every 3 months or more frequently. If benefits do not outweigh harms of continued opioid therapy, clinicians should optimize other therapies and work with patients to taper opioids to lower dosages or to taper and discontinue opioids.

Assessing Risk and Addressing Harms of Opioid use

8. Before starting and periodically during continuation of opioid therapy, clinicians should evaluate risk factors for opioid-related harms. Clinicians should incorporate into the management plan strategies to mitigate risk, including considering offering naloxone when factors that increase risk for opioid overdose, such as history of overdose, history of substance use disorder, higher opioid dosages (≥50 MME/day), or concurrent benzodiazepine use, are present.
9. Clinicians should review the patient's history of controlled substance prescriptions using state prescription drug monitoring program (PDMP) data to determine whether the patient is receiving opioid dosages or dangerous combinations that put him or her at high risk for overdose. Clinicians should review PDMP data when starting opioid therapy for chronic pain and periodically during opioid therapy for chronic pain, ranging from every prescription to every 3 months.
10. When prescribing opioids for chronic pain, clinicians should use urine drug testing before starting opioid therapy and consider urine drug testing at least annually to assess for prescribed medications as well as other controlled prescription drugs and illicit drugs.
11. Clinicians should avoid prescribing opioid pain medication and benzodiazepines concurrently whenever possible.
12. Clinicians should offer or arrange evidence-based treatment (usually medication-assisted treatment with buprenorphine or methadone in combination with behavioral therapies) for patients with opioid use disorder.

*All recommendations are category A (apply to all patients outside of active cancer treatment, palliative care, and end-of-life) except recommendation 10 (designated category B, with individual decision making required); see full guideline for evidence ratings.

Fig. 1.6 US Centers for Disease Control and Prevention Opioid Prescribing Guidelines. (Source: MMWR. Morbidity and Mortality Weekly Report. March 15, 2016. US Department of Health and Human Services/Centers for Disease Control and Prevention)

Unfortunately, the application of these guidelines in some cases has been much less nuanced, with some states and insurance companies moving to enact absolute limits on prescription opioid use. These sorts of black-and-white policies risk harming people who have been stably treated on chronic opioid therapy. Dramatic reductions in access to prescription opioids also risk pushing people with opioid use disorder toward the use of heroin or other illicit opioids obtained "on the street." The 2017 report by the National Academies of Science, Engineering, and Medicine acknowledged this potential negative impact of supply-focused policies through "squeezing the balloon" where efforts to reduce the misuse of prescription opioids may actually increase other use of potentially even more dangerous opioids, such as heroin [11]. An example of this was the reformulation of OxyContin into a deterrent formulation intended to prevent misuse, which was associated with a transition to heroin use and an increase in heroin-related overdose deaths.

A further strategy to reduce exposure to prescription opioids was to reduce accessibility via community-based "take back" programs. These initiatives were designed so that individuals could drop off unused opioid medication at local police stations or increasingly at pharmacy "drop boxes" at no cost and no questions asked.

Demand Reduction: Prevention, Treatment, and Recovery Support Services

A number of evidence-based medications, psychosocial interventions, and recovery support services are available to help people suffering from opioid use disorders. Particularly effective in treating opioid use disorder are the agonist therapies methadone and buprenorphine, with the latter being combined with naloxone to create a therapeutic hybrid buprenorphine/naloxone marketed as "Suboxone." The most scientifically rigorous systematic quantitative reviews of placebo-controlled randomized trials indicate that buprenorphine is an effective medication in the maintenance treatment of heroin addiction, retaining people in treatment at any dose above 2 mg and suppressing illicit opioid use (at doses 16 mg or more) based on placebo-controlled trials. However, compared to methadone, buprenorphine retains fewer people when doses are flexibly delivered and at low fixed doses. If fixed, medium or high, doses are used, buprenorphine and methadone appear no different in effectiveness (retention in treatment and suppression of illicit opioid use) [12]. For prescription opioid addiction, similar results have been found (although the quality of evidence is not as good as it is for heroin addiction). Another rigorous systematic review of clinical trials, for example, found little to no difference between how well methadone and buprenorphine worked to keep people in treatment, to reduce opioid use, or in the side effect profile. The conclusion was that buprenorphine keeps more people in treatment, reduces opioid use, and has fewer side effects compared to detoxification or psychological treatment alone [13].

Antagonists, such as naltrexone, which block the mu-opioid receptor (instead of agonizing it like buprenorphine or methadone), thus preventing the reinforcing effects from opioids should they be used, have been tested among individuals with opioid use disorder. A systematic review of oral naltrexone found it be no better than

placebo or detoxification [14], presumably due to the lack of compliance with oral/daily administration. Once per month injectable extended-release naltrexone, in contrast, fares better, especially when it is administrated following initial medically supervised withdrawal to achieve seven to ten days of opioid abstinence. In intent-to-treat analyses, buprenorphine is more effective as a treatment for opioid use disorder; however, among the subset of patients who are able to complete medically supervised withdrawal, extended-release naltrexone has similar efficacy to buprenorphine in preventing relapse to illicit opioids [15, 16].

Consequently, in sum, there is overall generally good quality, coherent, and consistent experimental evidence supporting agonist, and to a lesser degree, antagonist, medication treatment for opioid use disorder. These are among the most effective treatments for any substance use disorder and should be considered first-line approaches in addressing opioid addiction.

Detoxification, stabilization, and psychological treatments (e.g., cognitive-behavioral therapy [CBT], twelve-step facilitation [TSF], and motivational interviewing [MI]-based interventions) without medications tend not to perform as well, and while popular, little is known about the efficacy of mutual-help organizations, such as SMART Recovery or Narcotics Anonymous, in facilitating and aiding OUD remission [17]. Adding specialized addiction counseling (e.g., CBT for addiction) to agonist medication, therapies that already come with brief 20–45-minute prescriber counseling and checkup—a manualized intervention known as "medical management" (MM)—have not been shown to enhance outcomes among OUD patients [18]. The failure to show additional benefit for specific addiction counseling on top of MM and medications (e.g., buprenorphine/naloxone) may be because MM is likely to mobilize the same kinds of therapeutic mechanisms (e.g., recovery motivation, active coping, increased recovery self-efficacy) that are mobilized by all active interventions [19, 20] and, thus, adding an additional specific intervention does not confer additional benefit. Similar kinds of null effects have been found in other studies where psychosocial interventions are increased in intensity (e.g., from 5 hours of therapeutic contact to 20 hours) but do not confer increased therapeutic benefit [21]. There is some preliminary evidence for potential therapeutic synergy from extended community-based interventions, such as Narcotics Anonymous (NA) participation in addition to buprenorphine or methadone [22]. At least one large observational study found that opioid use disorder patients on buprenorphine/naloxone (Suboxone), who engaged more in NA, had significantly better retention on the medication and higher abstinence rates [23]. More studies are needed in these areas to help determine who in particular may benefit from these additional community services to aid long-term remission and recovery.

A large number of individuals suffering from OUD come into contact with the treatment system via the criminal justice system. There has been a growth in so-called drug courts which have been increasingly used to help individuals with opioid use disorder access treatment rather than jail or prison [24, 25]. Compared to adjudication as usual or jail/prison time, drug courts provide access to opioid use disorder treatment and use a combination of monitoring and oversight in treatment to help offenders initiate remission and gain a foothold in

recovery. Evidence on these entities specifically are somewhat mixed [24, 25], but the quality of evidence is low.

There is some evidence that mandated treatment via the criminal justice system produces outcomes as good as or better than more "voluntary" patients. Rather than suggesting that incarceration or mandated treatment is superior to increased accessibility of voluntary treatment, these better outcomes may be because the criminal justice system facilitates treatment exposure earlier than would normally happen if individuals are left to their own devices, and such mandated patients tend, thus, to have better prognoses [26] and shorter time to remission [27, 28]. In general, the criminal justice system can play a powerful role in truly diverting individuals with OUD into treatment settings rather than detention, incarceration, or correctional supervision such that they begin the treatment process earlier.

Recent recognition of the intransigence of the current opioid crisis by law enforcement officers has led to innovative efforts by some police departments (e.g., Gloucester, MA) to facilitate access to treatment rather than criminal prosecution for individuals with addiction who present themselves at the police station. In Burlington, VT, a partnership between the police department, the mayor's office, the hospital, and the state attorney has sought to increase access to medication treatment for opioid use disorder including not prosecuting people for buprenorphine diversion. This type of approach from a police department and state attorney represents a massive philosophical shift and a recognition by law enforcement that lower threshold access to care, rather than punishment, is the key to addressing the ongoing crisis. These types of approaches to be spontaneously initiated by law enforcement reflect a recognition and increased appreciation of potentially ineffective, traditional, law enforcement approaches to addressing opioid use disorder.

From the standpoint of preventing morbidity and mortality for those with opioid use disorder, demand-focused interventions are by far the most effective. Treatment with medications such as buprenorphine and methadone has been shown to reduce mortality risk by between 50% and 80% [29]. Engagement in treatment and ongoing recovery supports reduces the likelihood of ongoing opioid use and its associated harms [22, 30, 31]. Lowering the barriers to treatment access through integrating addiction care into the medical system, ensuring insurance parity for services, and restructuring care models to focus on engagement and retention increase the likelihood that individuals with opioid use disorder will get care and reduce or stop ongoing opioid use [30].

Importantly, given the high degree of heterogeneity in clinical histories and presentations, and clinical course of opioid and other substance use disorders, it is often stated that "one size does not fit all." Many patients, for example, will not take medications despite their proven efficacy. For these patients, proven alternatives should be on the menu of additional options so that patients can choose another option that could help the patient engage and improve their quality of life. These may take the form of long-term residential options such as recovery housing [32], which have shown to be helpful and cost-effective along with the use of other recovery supports such as recovery community [33]. Such centers can assist in helping people get jobs and get connected to other recovery support services (e.g., recovery coaching) that can help sufferers build recovery capital and instill hope for the future.

Harm Reduction Strategies

Not all those with opioid use disorders are able or want to stop using opioids for a variety of reasons. For such individuals, a variety of services and strategies have been developed and increasingly deployed to positive effect in many countries around the world. These are designed to reduce overdose deaths as well as lower the potential for transmission of infectious diseases, such as HIV and hepatitis C. Quantitative reviews including meta-analyses support the implementation of such approaches [34, 35]. In the United States these have taken the form of syringe service programs, overdose education and naloxone ("Narcan") distribution programs, and lower threshold treatment models. Other countries have expanded harm reduction even further to offer supervised injection facilities and supervised prescription heroin and injection programs (e.g., in the United Kingdom; [31]). While cities in the United States have begun exploring the possibility of opening supervised injection facilities, strong opposition from the federal government remains. Evidence mostly from studies conducted in two cities, Vancouver, Canada, and Sydney, Australia, supports the public health utility of safe injection facilities [36], but findings are somewhat mixed in high-quality studies in this domain. That said, there is no evidence that these facilities increase rates of drug use in any capacity. More research, however, is needed to understand the clinical and public health benefits related to these facilities and who in particular is likely to benefit from them.

An initial wave of rising prescription opioid use and related overdose deaths has since been surpassed by a second wave of heroin use and overdose and then illicitly manufactured fentanyl and related death. Addressing the crisis requires an understanding and application of public health models which focus not only on supply reduction but importantly also on addressing demand through treatment and harm reduction.

Conclusions and Future Directions

Most middle- and high-income countries globally have become largely inured to the endemic premature mortalities related to more commonly used substances such as alcohol and tobacco. While these account for a much larger number of deaths and economic and social harms than opioids each year, the devastation wreaked by these substances, their casualties, and the associated blood and tears are all relatively willingly absorbed into the social fabric. These are not news. What is news is the rapid rise and spread of new substance-induced casualties and the tragic premature end to so many additional lives as a result of opioid overdose. While much needs to be done to address all substance use disorders, the novelty and surge of this particular epidemic begs the question as to how such new tragedies can be prevented in future. What can be learned from this crisis and put to good use for the benefit of future generations?

To begin, there was a clear disconnect between clinical practice and adequate science on safety and addiction potential regarding new prescription opioids. There

has been an often-cited gap between practice and science for addiction treatment services, whereby practitioners either are not knowledgeable about or otherwise fail to implement science-based "best practices." In this instance, however, it was a slightly different take on this criticism. Providers believed or were led to believe that these potent medications were in fact safe from a *scientific standpoint*. So, it was not the traditional "research–practice gap" that was to blame, but rather the misbelief, misinterpretation, and/or misapplication of the science. It is easy to see this in retrospect, but no one predicted it. The blithe acceptance and unquestioning citation by the medical community of a completely inadequate single publication regarding justification for safety were seized upon by the pharmaceutical industry. With seeming scientific assurance, the industry was able to deploy their significant public relations machinery to exert considerable weight and influence and subsequently increase prescribing of potent opioid medications to address pain. This effort was potentiated by a humane medical infrastructure push to address the debilitating human misery caused by acute and chronic pain. For a few years, while the focus lay on ensuring practitioners were assessing "the fifth vital sign," and prescribing accordingly, the waves on the surface appeared to be no cause for alarm. Yet, an invisible undertow was present and gathering momentum. This undercurrent would ultimately begin to sweep hundreds of thousands out to sea to drown beyond their depth, with even bigger waves of heroin and fentanyl to follow.

Going forward, one potential way to prevent this from happening again would be to create an annual independent scientific review and mandatory practitioner continuing education course on the science base for any new medications that have been adopted into health-care systems. This should be ordained as a national standard. In addition, continuing practice-based measurement and monitoring of the therapeutic effects of new medication implementation should be a part of routine care so that we move toward a system of "measurement-based practice" [37] that helps enhance quality and monitors safety in order to continually improve addiction health services. In addition, stricter regulations on the pharmaceutical industry to prohibit direct-to-consumer marketing and drastically curtail marketing to and conflicts of interest with physicians are desperately needed.

Another factor that needs to be addressed to prevent such a tragedy in the future is stigma and discrimination. The stigma and discrimination that pervades addiction meant a lethargic response to a rapidly growing public health crisis which, for almost any other health threat that might kill only a fraction of the number killed by the opioid overdose crisis, would have been met with greater alarm and more immediate and adequate appropriation from state and federal entities. A national response like those seen internationally to stem the threat from Ebola (Ebola virus disease [EVD]) or severe acute respiratory syndrome (SARS) would have curtailed this crisis. Instead, while the alarm bell was ringing there was a cultural and political deafness underwritten by prejudice against those suffering from addiction. This allowed an emerging crisis to grow and spread, change shape, and increase its toll until not a day passed without mention of the "opioid overdose crisis" on media channels of every political orientation and flavor. Only when it was realized that the overdose crisis kills equally across party lines, and the tears from dozens of bereaved mothers had moistened the

benches of congress, did government begin to come together to act; but it was too little, too late, for hundreds of thousands of families. The pervasive impact of racism in our society's response to addiction crises and people who use drugs cannot be overemphasized. In past drug epidemics when the communities most deeply affected were black and Hispanic/Latino, the overwhelming response was a tough-on-crime approach that resulted in mass incarceration. The notion that the current crisis is in fact a public health issue was strongly influenced by the narrative of the innocent white victim, deserving of compassion rather than punishment. Addressing these pervasive stigmatizing attitudes through increasing education about the nature of opioid and other substance use disorders, shifting our language and terminology so that it more accurately reflects the neurological and medical nature of these conditions [38, 39], and increasing the personal testimony from the millions already in recovery [40] who are willing to speak out and demonstrate that recovering "addicts" are like everyone else, are ways likely to help reduce the prejudice, stigma, and discrimination that has retarded and undermined an adequate, rapid, response to the current crisis.

Finally, ideological stigma against proven effective medications also has meant too many have suffered and lost their lives when both might well have been avoided had providers, and politicians, understood the science on the effectiveness of these medications. Methadone, buprenorphine/naloxone, and extended-release naltrexone have among the strongest data of any intervention for any substance use disorder supporting their therapeutic benefits. Yet, people taking these highly effective medications remained misunderstood and, ironically, re-stigmatized as being "still using." Little attention was paid to acknowledging the clinical scientific data demonstrating that these medications dramatically reduce the risk of overdose death and enhance remission rates for OUD. Such prejudices against addiction treatment and medications in particular are driven by ignorance of the evidence base and misunderstanding of the nature of opioid addiction.

In sum, there are several hard lessons that might be learned from the rise and spread of the current opioid addiction and overdose death crisis. These pertain to recognizing the value of clinical science and the need to translate and understand it properly as well as respect it and the need to address stigma and misunderstanding both outside and inside the addiction field. Socially and culturally, attention to addiction has perhaps never been higher. The question for the future will be whether these grave and tragic lessons learned will be taken to heart and the structural changes made to prevent such crises from recurring in the future.

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Epidemiology: Opioid Use and Related Disorders

2

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Abbreviations

CDC	Centers for Disease Control and Prevention
CHIP	Children's Health Insurance Program
DSM	Diagnostic and Statistical Manual of Mental Disorders
ER	Extended-release
ICD	International Classification of Diseases
LA	Long-acting
MME	Morphine milligram equivalents
MTF	Monitoring the Future
NSDUH	National Survey on Drug Use and Health
YRBS	Youth Risk Behavior Survey

Overview of the Medical Complications of Opioid Use and the Opioid Overdose Epidemic

The estimated global all-cause mortality rate among individuals who use illicit opioids regularly or are known to have an opioid use disorder is approximately two per 100 person-years, a rate that is nearly 15 times higher than the general population [1]. These high mortality rates may be attributed to complications of opioid use, opioid use disorder, and injection drug use. Among all medical complications of opioid use and opioid use disorders, overdose is the most common cause of death (pooled overdose death rate of 0.65 per 100 person-years), followed by trauma (0.25

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deaths per 100 person-years) and suicide (0.12 deaths per 100 person-years) [1]. Other medical complications that contribute to opioid-related morbidity and mortality include infectious diseases, particularly skin and soft tissue infections [2–4], infective endocarditis [5], HIV, hepatitis B virus infection, and chronic active hepatitis C (Table 2.1) [6–10]. These infectious complications tend to be due to injection drug use, particularly in the context of limited access to sterile syringes and needles and skin cleaning supplies. For example, in 2015, an HIV outbreak in Indiana was linked to injection use of pharmaceutical opioids [7]. Neonatal abstinence syndrome is another important complication of opioid use and can result from maternal prescribed use, illicit use, and opioid agonist treatment.

The United States is in the midst of an opioid epidemic characterized by unprecedented increases in overdose fatality rates [11]. Overdose deaths involving opioids increased by 490% between 1999 and 2017 [11]. Alongside overdose deaths, rates of medical complications of opioid use, such as neonatal abstinence syndrome, have also been increasing [4, 6, 12–16]. Opioids are involved in the majority of overdose deaths; of the nearly 70,000 drug overdose deaths in the United States in 2017, more than two thirds (n = 47,600) involved a pharmaceutical opioid (alternatively called prescription opioids, opioid analgesics, opioid pain relievers, and natural/semisynthetic opioids) and/or illicit opioid (i.e., heroin or illicitly manufactured synthetic opioids excluding methadone, such as fentanyl) [11].

The opioid overdose epidemic has been characterized by three phases [17, 18]. While it is important to recognize that heroin overdose was already an important public health problem in the 1980s and early 1990s [19], the mid-to-late 1990s were characterized by marked increases in pharmaceutical opioid overdoses, generally attributed to increased prescribing [20]. These pharmaceutical overdoses may have partly led to reversal in life expectancy gains among US white middle-aged adults [21]. After steadily increasing each year from 1999 to 2011, rates of pharmaceutical opioid overdose deaths appeared to stabilize somewhat as increasing efforts to restrict opioid prescribing were made. However, by 2016, pharmaceutical opioid overdose rates increased by greater than 10% from the prior year [11]. Thus, while pharmaceutical opioid overdoses characterized the "first" phase of the epidemic, and heroin and illicitly manufactured fentanyl characterize the "second" and "third"

Table 2.1 Medical complications of opioid use

Neonatal abstinence syndrome [12–14, 16]
Fractures [165, 166]
Gastrointestinal effects [167–169]
Cardiovascular events (limited evidence) [170, 171]
Injection drug use-related complications
Skin and soft tissue infections [2, 4]
Infective endocarditis [5]
HIV [6–9]
Hepatitis B and C [8, 10, 172]

phases of the epidemic, respectively, heroin overdoses predated the first phase, and pharmaceutical opioids continue to be an important contributor to the second and third phases.

The second phase of the epidemic is thought to have started during 2010–2011, when the number of deaths attributed to heroin overdose began to increase. Between 2012 and 2017, there was a more than 2.5-fold increase in the heroin overdose mortality rate, and by 2017, nearly 15,500 opioid overdose deaths involved heroin [11].

The third phase of the epidemic, which began around 2013, was characterized by increasing overdose rates attributed to synthetic opioids, which include fentanyl and fentanyl analogs. Between 2015 and 2016, the rate of overdose deaths involving synthetic opioids doubled, and 2016 was the first year that synthetic opioids were the most common type of opioid involved in overdose deaths [11, 18]. As of 2017, approximately 60% of opioid overdose deaths involved synthetic opioids other than methadone, predominately fentanyl [11].

The US opioid overdose epidemic has sometimes been portrayed as a rural, white epidemic by the media [22]. While there have been some notable differences in overdose rates by geographic region, gender, and racial/ethnic groups, most regions and populations have been affected by the epidemic and demographic and geographic overdose trends change rapidly. While nonmetro/rural communities and medium-small metropolitan areas have had high pharmaceutical opioid fatality rates, heroin overdose fatality rates have been higher in large metropolitan areas [11]. In each year of the epidemic, more men than women have died of opioid overdoses, but the gender difference is more pronounced for synthetic opioid and heroin overdoses than pharmaceutical opioid overdoses [11]. In the late 1990s and early 2000s, heroin overdose fatality rates were slightly higher for individuals of non-Hispanic black and Hispanic race/ethnicity; more recently, overdoses involving heroin have been increasing in these groups as well as among non-Hispanic whites. In contrast, for most years between 1999 and 2017, overdose death rates related to pharmaceutical and synthetic opioids were higher among non-Hispanic white than non-Hispanic black and Hispanic racial/ethnic groups [11]. American Indian and Alaska Native groups have had particularly high rates of pharmaceutical opioid overdose [18].

Drivers of the Opioid Overdose Epidemic

Opioid Prescribing

Opioids have been used for medicinal and recreational purposes for thousands of years. Acceptance of the use of opioids to manage pain, particularly chronic non-cancer pain, has waxed and waned throughout history [23, 24]. During the late twentieth and early twenty-first centuries, the development and widespread marketing of new opioid analgesics, such as extended-release oxycodone (OxyContin™), drove more liberal prescribing of opioid analgesics. These analgesics were widely but inaccurately believed to have low addiction potential [25]. Pain was also

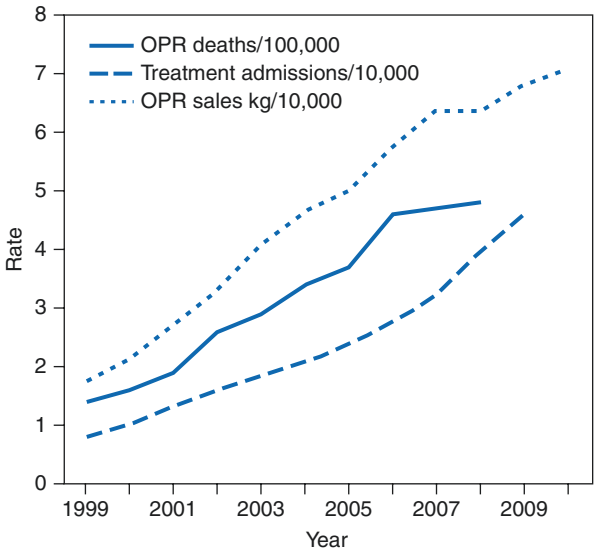

Fig. 2.1 Rates of opioid pain reliever (OPR) overdose death, OPR treatment admissions, and kilograms of OPR sold, United States, 1999–2010. (From: US Centers for Disease Control and Prevention [28])

increasingly recognized as an inadequately treated public health problem [26, 27]. Between 1999 and 2010, sales of opioid pain relievers quadrupled (Fig. 2.1); this growth in prescribing was paralleled by increases in opioid-related overdose deaths and opioid use disorder treatment admissions [28].

In the wake of the opioid overdose and addiction crisis, federal, state, and local organizations sought to foster safer prescribing of opioid analgesics [29–32]. Around 2012–2013, overall opioid prescribing rates began to decrease (Fig. 2.2) [33]. For example, the opioid prescribing rate decreased from approximately 81 prescriptions per 100 persons in 2012 to 59 prescriptions per 100 persons in 2017. Prescriptions of high-dosage opioids, defined as ≥90 morphine milligram equivalents [MME]/day, decreased by more than half between 2008 and 2017 [34] (Fig. 2.2). While lower dose prescriptions are consistent with prescribing guidelines [31], trends in days' supply suggest there were greater reductions in brief prescriptions compared with longer prescriptions. For example, from 2006 to 2017, opioid prescriptions of <30 days' supply fell from 55 to 34 prescriptions per 100 persons, while prescriptions for ≥30 days' supply grew [33]. Across a variety of pain etiologies, increasing days' supply is associated with increased risk of taking opioids long term [35].

Although national opioid prescribing rates have decreased, prescribing practices vary by geographic area. In county-level analyses between 2010 and 2015, Guy and colleagues [36] found that overall opioid prescribing rates fell in about half of counties, and high-dose prescribing rates fell in 87% of counties. The average opioid prescribing per capita in the top-prescribing counties in 2015 was six times that in the lowest prescribing counties. Counties with a larger percentage of non-Hispanic

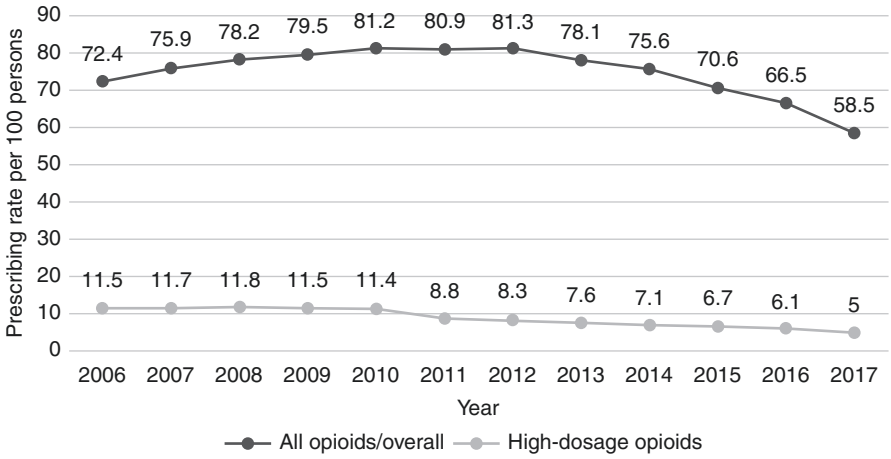

Fig. 2.2 Annual prescribing rates by overall and high-dosage (≥90 MME/day) opioid prescriptions, 2006–2017. (From: US Centers for Disease Control and Prevention [34])

whites; higher prevalence of diabetes, arthritis, and disability; more dentists and physicians per capita; higher suicide rates; micropolitan status (i.e., town/city; non-metro); and higher rates of uninsured, unemployment, and Medicaid enrollment tended to have higher opioid prescribing [36]. Rolheiser and colleagues found that Congressional districts with high prescribing rates were concentrated in the South, Appalachia, and rural West and that low-prescribing districts were concentrated in urban centers [37]. At the state/territory level, Centers for Disease Control and Prevention (CDC) data show that opioid prescribing rates in 2017 ranged from a low of 29 prescriptions per 100 persons in the District of Columbia to a high of 107 prescriptions per 100 persons in Alabama; similar variability was observed for high-dosage opioids [33].

The reasons for variable opioid prescribing are diverse. Providers' prescribing practices are likely to be shaped by the characteristics of the patient populations they serve, such as the prevalence of painful conditions. Geographic differences in provider education and training and policies related to opioid prescribing may also contribute. However, a lack of consensus about appropriate opioid use has been described as a major source of the geographic variation in prescribing [36].

Several studies conducted over the past 25 years have identified patient race and ethnicity as drivers of variable provider pain management practices. These studies have suggested that patients who are non-Hispanic white are more likely to be prescribed opioids in emergency and other care settings than African Americans, Hispanics, and other racial and ethnic groups [38–42]. In contrast, an analysis of Medical Expenditure Panel Survey data for adults with moderate or severe noncancer pain showed that, in 2015, the percentage of individuals who identified as non-Hispanic black who used opioids was similar to that of individuals who identified as

non-Hispanic white (23% of individuals in each group used opioids) [43]. The authors also found that the percentages of adults who used opioids to manage moderate or severe noncancer pain increased across racial and ethnic groups between 2000 and 2015 [43].

In recent decades, opioid prescribing to women has typically been higher than prescribing to men [44, 45]; as of 2016, the rate of opioids filled or refilled was 22 per 100 persons for women and 16 per 100 persons for men [46]. Women are also more likely to be given higher dosages of opioids and use them for a longer duration of time [44]. Sex differences in opioid receipt may be related to a higher prevalence of painful conditions, differences in the experience of pain, and differences in pain reporting [47–50]. Consistent with previously observed differences in prescribing patterns across age groups, 2016 prescribing rates were highest among older individuals (29 prescriptions per 100 persons among those aged 65 and older compared with 12 prescriptions per 100 persons for those aged 15 to 19) [46].

Nonmedical Pharmaceutical Opioid Use

Data on substance use patterns are largely derived from household surveys, such as the National Survey on Drug Use and Health (NSDUH), and school-based surveys, such as Monitoring the Future (MTF) and the Youth Risk Behavior Survey (YRBS) [51–53]. Such surveys elicit information about past 30-day (i.e., current), past 12-month, and lifetime substance use, including frequency, duration, and reasons for use. These surveys may collect data on any use of prescription opioids, misuse or nonmedical use, or use that meets Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria for substance abuse or dependence (DSM-IV). For example, the NSDUH collects data on misuse of opioid pain relievers in any way not directed by a doctor, including use without a prescription of one's own; use in greater amounts, more often, or longer than told to take a drug; or use in any other way not directed by a doctor [19]. Such surveys are designed to be nationally representative and involve repeated (often yearly) collection of cross-sectional data. Data from these surveys can offer valuable insight on trends in the breadth of the opioid epidemic, the populations that are most affected, and hypotheses that need to be tested using individual-level longitudinal data. However, an important limitation of these surveys is that they rely on self-report. Individuals may be reluctant to report behaviors, such as substance use, that may be perceived as socially unacceptable, resulting in non-response bias or social desirability bias [54]. Therefore, these surveys may underestimate drug use within the populations studied. In addition, national household or school-based surveys do not typically reach individuals in juvenile detention, jails, and prisons, who are homeless, or who are otherwise institutionalized, in whom substance use is highly prevalent [55–57]. With these caveats in mind, below we describe some of the geographic and demographic trends in opioid use and use disorders that have driven the three phases of the opioid overdose epidemic.

As of 2017, 3.2 million Americans aged 12 and older (1.2%) had misused opioid pain relievers within the last 30 days, consistent with the definition of current misuse [58], and nearly 11.1 million people (4.1%) had misused opioid pain relievers in the past year. These estimates of current- and past-year opioid pain reliever misuse represent a decline from 2016 estimates [58]. Based on earlier surveys, which used a different methodology, the number of Americans aged 12 and older who had misused opioid pain relievers in the past year remained relatively steady during 2002–2005, increased somewhat during 2006–2010, and declined somewhat during 2011–2014, with a peak in 2006 (12.7 million or 5.1%) and nadir in 2014 (10.3 million or 3.9%) [59].

As of 2017, prevalence of current- and past-year opioid pain reliever misuse among individuals aged 12 and older is roughly even across geographic regions and county types "(i.e., large, small, nonmetro, urbanized, less urbanized, and completely rural counties) [58] (Table 2.2). As for differences by race and ethnicity, misuse prevalence is generally higher for those identifying as two or more races, American Indian/Alaska Native, or non-Hispanic white. Among youth, defined as ages 12–17, those identifying as Hispanic and non-Hispanic black/African American had higher prevalence of past-month and past-year misuse [58], perhaps an indication that the population of people who misuse opioid pain relievers is becoming increasingly diverse along racial and ethnic lines. Prevalence of opioid pain reliever misuse is higher in young adults aged 18–25 compared with other age groups. Misuse is also more common among males than females, except among younger youth aged 12–17, among whom the prevalence is slightly higher for girls [58].

Prevalence of misuse among those aged 12 and older is higher for those who are unemployed, have a household income below 100% of the federal poverty level, and either have Medicaid or Children's Health Insurance Program (CHIP) as their health coverage or no healthcare coverage (Table 2.3). Prevalence of opioid pain reliever misuse is also significantly higher in people with a history of mental illness. In people aged 18 and older, 9.7% of those with any mental illness and 14.3% of those with serious mental illness reported opioid pain reliever misuse in the past year [58].

According to the MTF survey, past-year misuse of opioid pain relievers among youth is declining (Fig. 2.3). Following a period of relatively steady increase since the early 1990s, prevalence of past-year misuse of opioid pain relievers was relatively flat between 2002 and 2004. Between 2004 and 2017, reported past-year misuse fell among 12th graders, from 9.5% to 4.2% [60]. By 2017, the proportion of all adolescents, defined as 8th, 10th, and 12th graders, who used OxyContin™ and Vicodin™ without a doctor's orders in the past year were 1.9% and 1.3%, respectively [60].[1] Past-year misuse of opioid pain relievers overall has also declined among young adults aged 19–28 following a peak level of misuse of 9.1% in 2008 [61].

[1] Specific questions related to use of Vicodin™ and OxyContin™ were added to the Monitoring the Future survey in 2002 as the prevalence levels of these drugs were thought to account for an upturn in use of the general class of narcotics other than heroin [21].

Table 2.2 Past-month and past-year misuse of opioid pain relievers, by geographic and demographic characteristics: percentages, 2017, NSDUH

	Past-Month Misuse				Past-Year Misuse			
	12+	12–17	18–25	26+	12+	12–17	18–25	26+
Total	1.2	0.9	1.8	1.1	4.1	3.1	7.2	3.7
Geographic Region								
Northeast	1.1	0.3	1.4	1.2	3.6	2.0	6.5	3.3
Midwest	1.1	0.8	1.9	1.0	4.2	2.8	7.4	3.9
South	1.3	0.9	2.3	1.2	4.0	3.1	7.5	3.5
West	1.1	1.2	1.3	1.1	4.4	4.0	6.9	4.0
County Type								
Large metro	1.1	0.8	1.6	1.1	3.9	3.0	6.4	3.7
Small metro	1.3	0.9	2.0	1.3	4.3	3.2	8.1	3.8
Nonmetro	1.2	1.0	2.3	1.0	4.0	3.3	8.1	3.5
Urbanized	1.1	0.6	2.3	1.0	3.9	3.1	7.4	3.4
Less urbanized	1.3	1.5	2.3	1.1	4.1	3.6	8.8	3.5
Completely rural	1.1	0.4	2.4	1.0	4.3	2.0	7.2	4.2
Hispanic Origin and Race								
Not Hispanic or Latino	1.2	0.8	1.9	1.1	4.1	2.9	7.2	3.7
White	1.3	0.8	2.0	1.2	4.4	2.9	7.9	4.0
Black or African American	1.0	1.0	2.1	0.8	3.5	3.6	6.3	2.9
American Indian or Alaska Native	1.4	0.6	1.9	1.4	5.7	2.6	5.0	6.4
Native Hawaiian or Other Pacific Islander	0.6	*	*	*	2.2	*	*	1.9
Asian	0.4	0.5	0.7	0.3	1.8	1.7	2.7	1.6
Two or more races	1.9	1.1	2.5	2.0	4.9	3.3	9.1	4.2
Hispanic or Latino	1.2	1.0	1.7	1.1	4.0	3.5	7.0	3.4
Sex								
Male	1.3	0.8	1.9	1.3	4.6	2.7	7.3	4.3
Female	1.1	1.0	1.8	1.0	3.6	3.5	7.0	3.1

Data from: Center for Behavioral Health Statistics and Quality. *= low precision [58]

Table 2.3 Past-month and past-year misuse of opioid pain relievers, by socioeconomic characteristics: percentages, 2017, NSDUH

	Past-Month Misuse				Past-Year Misuse			
	12+	12–17	18–25	26+	12+	12–17	18–25	26+
Total	1.2	0.9	1.8	1.1	4.1	3.1	7.2	3.7
Education								
< High school	da	da	2.2	1.0	da	da	8.1	3.4
High school graduate	da	da	2.1	1.1	da	da	7.6	3.6
Some college/associate's degree	da	da	2.0	1.5	da	da	7.5	4.6
College graduate	da	da	0.8	0.9	da	da	4.6	3.1
Current Employment								
Full-time	da	da	1.7	1.2	da	da	7.5	4.1
Part-time	da	da	1.5	1.3	da	da	6.9	3.6
Unemployed	da	da	3.8	2.5	da	da	9.1	7.1
Other	da	da	1.7	0.8	da	da	6.0	2.8
Poverty Level								
Less than 100%	1.6	1.0	2.0	1.5	5.1	3.8	6.9	4.9
100–199%	1.4	1.1	2.3	1.2	4.2	3.3	7.4	3.6
200% or more	1.0	0.7	1.6	1.0	3.8	2.7	7.3	3.5
Health Insurance								
Private	0.9	0.7	1.5	0.9	3.5	2.6	6.8	3.2
Medicaid/CHIP	1.8	1.2	2.1	1.9	6.0	3.9	8.1	6.1
Other	0.8	1.0	2.4	0.7	2.7	4.0	8.0	2.5
No coverage	2.3	0.7	2.9	2.2	6.1	2.8	7.8	5.9

Data from: Center for Behavioral Health Statistics and Quality [58]
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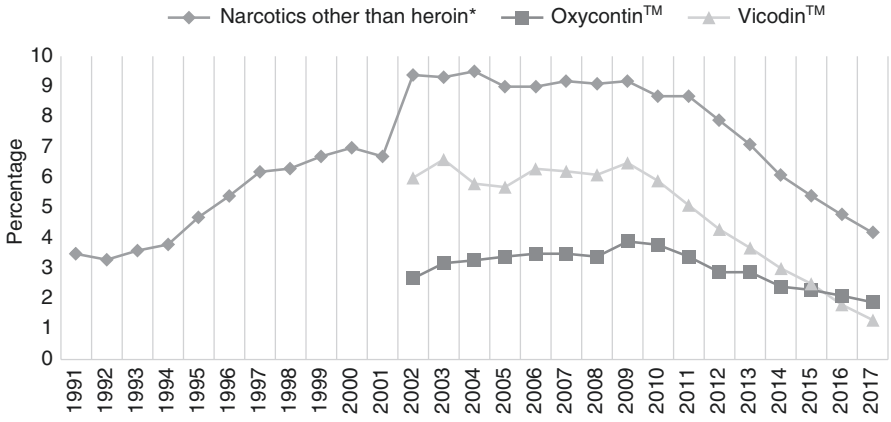

Fig. 2.3 Past-year use without a doctor's orders of narcotics other than heroin, OxyContin™, and Vicodin™ in 8th, 10th, and 12th graders, Monitoring the Future, 2017. *Includes 12th grade students only; data were not reported for 8th and 10th graders due to questionable validity. Narcotics other than heroin includes Oxycontin™ and Vicodin™. (Data from Miech RA, et al. [60])

Among 12th graders, the MTF study reports a prevalence of current use of opioid pain relievers without a doctor's orders of 1.6% in 2017, down from a peak of 4.3% in 2004 [60]. In contrast, past-year misuse has declined more moderately or increased slightly for those aged 35 and older [61].

Despite some declines in current- and past-year misuse of opioid pain relievers, more than 2 million people initiated opioid pain reliever misuse in 2017 [58]. Misuse of opioids is associated with a high risk of overdose and death [62–64]; despite these risks, many people do not view opioid pain reliever misuse as a high-risk behavior. For example, roughly a quarter of individuals aged 18–30 in 2016 did not see regular misuse of opioid pain relievers as posing a great risk of physical or other harm, with little change in risk perception since 2012 [61].

Prevalence of opioid pain reliever misuse is considerably higher in people who use other substances than in the general population. As would be expected, more than two-thirds of people who reported past-year heroin use also misused opioid pain relievers in 2017 [58]. Past-year misuse of opioid pain relievers is also more prevalent among people who reported past-year use of methamphetamine, hallucinogens, cocaine, and inhalants and, to a lesser extent, marijuana, tobacco products, and alcohol (Fig. 2.4).

Friends and family members are among the most common sources of misused opioid pain relievers, despite increased efforts to educate the public about safe storage and disposal of, and the importance of not sharing, prescription opioids [58, 65, 66]. NSDUH data suggest that more than 53% of individuals who misused opioid pain relievers in 2017 obtained them the last time from a friend or

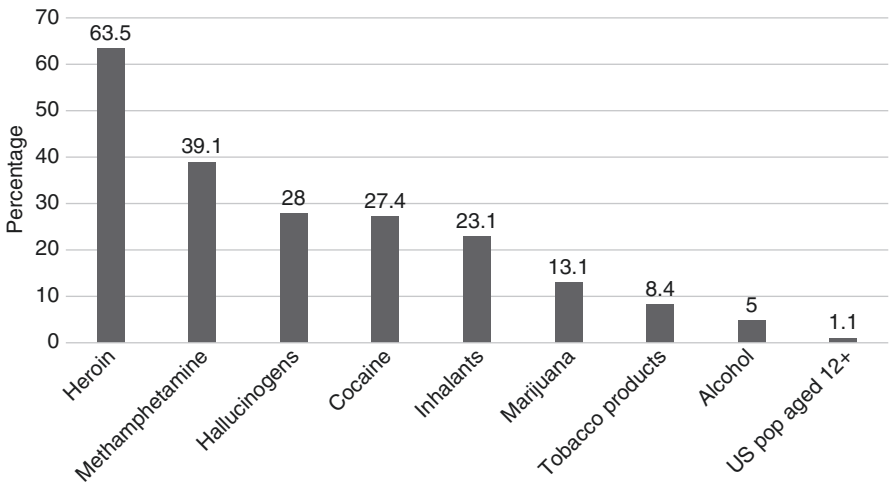

Fig. 2.4 Percentage of individuals aged 12 and older who in the past year engaged in any misuse of pain relievers, 2017, NSDUH. (Data from: Center for Behavioral Health Statistics and Quality [58])

relative, either for free (38.5%) or by purchasing them or taking them without asking (14.6%) [58]. Healthcare providers are also a frequent direct source of misused opioids. Compared with the 6% of people who misused opioid pain relievers in the past year and who obtained the drugs the last time by purchasing them from a drug dealer or stranger, over one-third acquired the drugs by prescription from one doctor [58]. Among those who reported past-year misuse, youth and young adults are somewhat more likely than older adults to take opioid pain relievers from friends or family members without asking or to purchase them from a drug dealer or stranger [58].

Individuals may have multiple reasons for misusing opioid pain relievers, although for many a primary motivation is an effort to ease physical pain. Misuse in this context might include taking opioid pain relievers at higher dosages or more often than prescribed in hopes of attaining a stronger pain-relieving effect and/or taking them without a prescription from a healthcare provider. In the NSDUH, more than 60% of respondents who misused opioid pain relievers in the past year reported that the main reason for their most recent misuse was to relieve physical pain (Fig. 2.5). For others, specific psychoactive effects other than pain relief are the primary motivators for opioid pain reliever misuse, such as getting high or helping them relax or relieve tension [58]; however, some of these effects can be difficult to disentangle entirely from the analgesic properties of opioids, since pain and tension are highly correlated.

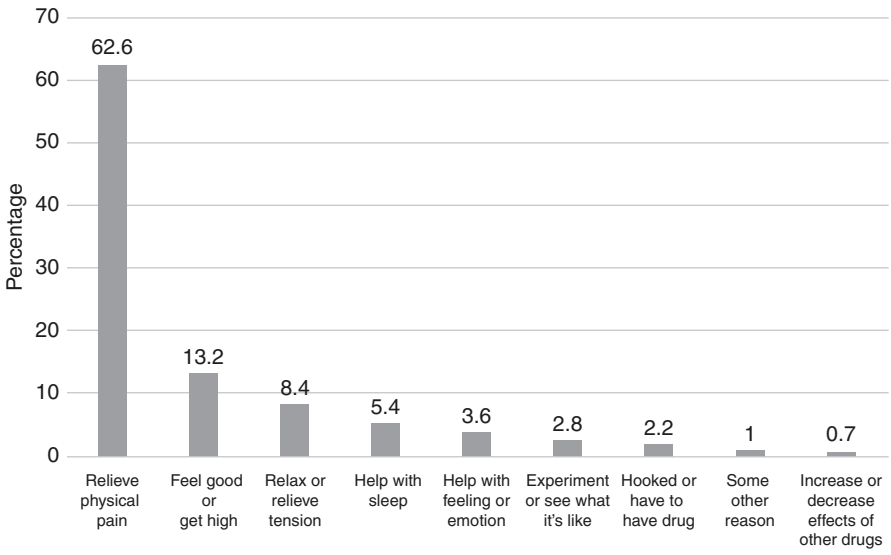

Fig. 2.5 Main reason for the most recent prescription pain reliever misuse among people aged 12 and older who misused prescription pain relievers in the past year, percentage (of 11.1 million people), 2017, NSDUH Percentages do not add to 100% due to rounding. (Data from: Center for Behavioral Health Statistics and Quality [58])

Heroin Use

Historically, the prevalence of heroin use in the United States has been low relative to use of other drugs, but the number of people using heroin has generally been on an upward trend for the last decade (Table 2.4) even though a large majority of people view both experimental and regular use of heroin as dangerous [58, 60, 61]. In 2017, about 494,000 Americans aged 12 or older (0.2%) reported current heroin use, more than the number for each year from 2005 to 2016. About 886,000 (0.3%) people aged 12 or older reported heroin use in the past year. This estimate is higher than those for each year between 2005 and 2013 and similar to those for 2014–2016. For each year from 2005 to 2017, the number of individuals who engaged in current and past-year heroin use was highest among adults aged 26 and older, while young adults aged 18 to 25 had the highest percentages of users. In 2017, 81,000 people aged 12 or older initiated heroin use, a decrease since 2016 [58].

Lifetime heroin use prevalence can be used to explore differences in use patterns across smaller subgroups of the population. For instance, according to the YRBS, lifetime heroin use in 2017 was higher among high school students who said they were not sure of their sexual identity (7.7%) compared with students who identified as heterosexual (1.1%) or gay, lesbian, or bisexual (3.5%). In addition, lifetime heroin use was higher in high school students who said their sexual contacts included individuals of the same sex only or of both sexes (6.6%) than students who said they had no sexual contacts (.3%) or that their sexual contacts included individuals of the opposite sex only (1.7%) [66].

Approximately equal proportions of adolescents with a lifetime history of heroin misuse used heroin with and without a needle (0.4% each) in 2017 [60]. Nearly eight times more people who reported past-month cigarette use than who did not Nearly eight times more people who reported past-month cigarette use than who did not reported they also used heroin in the past month (440,000 vs 55,000) [58].

Opioid Use Disorders

Recurrent drug use can lead to a substance use disorder, which impairs health, function, and the ability to meet responsibilities at work, school, and home [58]. According to the NSDUH, the overall number of Americans aged 12 or older who met DSM-IV criteria for opioid abuse or dependence due to opioid pain relievers in the past year decreased by about 360,000 between 2015 and 2017 (Table 2.5) [58]. Based on the earlier NSDUH questions, which are not comparable to 2015–2017 questions, between 1.55 and 2.06 million Americans met criteria for DSM-IV opioid abuse or dependence due to pain relievers each year during 2005–2014 [59].

The number of Americans aged 12 or older who met criteria for opioid use disorder related to heroin in the past year has substantially increased over the past decade, growing from 227,000 in 2005 to 652,000 in 2017 (Table 2.5) [58]. As is the case with the recent increase in heroin use, the growth in heroin use disorder may in part be a result of an upsurge in exposure to opioids through prescribing during the late 1990s and early

Table 2.4 Past-month and past-year heroin use, by age group, 2005–2017: numbers (in thousands) and percentages, 2005–2017, NSDUH

	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
Past-month Heroin Use													
12+	136 (0.1)	339 (0.1)	161(0.1)	213 (0.1)	193 (0.1)	239 (0.1)	281 (0.1)	335 (0.1)	289 (0.1)	435 (0.2)	329 (0.1)	475 (0.2)	494 (0.2)
12–17	15 (0.1)	16 (0.1)	3 (0.0)	14 (0.1)	13 (0.1)	8 (0.0)	15 (0.1)	*	13 (0.1)	16 (0.1)	5 (0.0)	3 (0.0)	2 (0.0)
18–25	59 (0.2)	55 (0.2)	49 (0.1)	76 (0.2)	67 (0.2)	90 (0.3)	107 (0.3)	138 (0.4)	92 (0.3)	82 (0.2)	88 (0.3)	88 (0.3)	102 (0.3)
26+	62 (0.0)	268 (0.1)	109 (0.1)	124 (0.1)	112 (0.1)	141 (0.1)	159 (0.1)	197 (0.1)	185 (0.1)	337 (0.2)	236 (0.1)	383 (0.2)	390 (0.2)
Past-year Heroin Use													
12+	379 (0.2)	560 (0.2)	373 (0.2)	455 (0.2)	582 (0.2)	621 (0.2)	620 (0.2)	669 (0.3)	681 (0.3)	914 (0.3)	828 (0.3)	948 (0.4)	886 (0.3)
12–17	37 (0.1)	37 (0.1)	24 (0.1)	41 (0.2)	34 (0.1)	28 (0.1)	54 (0.2)	31 (0.1)	31 (0.1)	28 (0.1)	21 (0.1)	13 (0.1)	14 (0.1)
18–25	159 (0.5)	147 (0.4)	142 (0.4)	149 (0.5)	183 (0.5)	211 (0.6)	230 (0.7)	272 (0.8)	244 (0.7)	268 (0.8)	217 (0.6)	227 (0.7)	214 (0.6)
26+	184 (0.1)	376 (0.2)	207 (0.1)	265 (0.1)	364 (0.2)	382 (0.2)	336 (0.2)	366 (0.2)	406 (0.2)	618 (0.3)	591 (0.3)	708 (0.3)	658 (0.3)

Data from: Center for Behavioral Health Statistics and Quality [58]. * = low precision

Table 2.5 Heroin use disorder and pain reliever use disorder in past year, by age group: numbers (in thousands) and percentages, 2005–2017, NSDUH

	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
Past-year Heroin Use Disorder													
12+	227 (0.1)	324 (0.1)	214 (0.1)	283 (0.1)	369 (0.1)	361 (0.1)	426 (0.2)	467 (0.2)	517 (0.2)	586 (0.2)	591 (0.2)	626 (0.2)	652 (0.2)
12–17	9 (0.0)	12 (0.0)	8 (0.0)	17 (0.1)	18 (0.1)	7 (0.0)	30 (0.1)	20 (0.1)	10 (0.0)	18 (0.1)	6 (0.0)	1 (0.0)	4 (0.0)
18–25	89 (0.3)	66 (0.2)	77 (0.2)	99 (0.3)	104 (0.3)	119 (0.3)	139 (0.4)	173 (0.5)	182 (0.5)	168 (0.5)	155 (0.4)	152 (0.4)	165 (0.5)
26+	129 (0.1)	245 (0.1)	129 (0.1)	167 (0.1)	246 (0.1)	236 (0.1)	256 (0.1)	274 (0.1)	325 (0.2)	400 (0.2)	430 (0.2)	473 (0.2)	483 (0.2)
Past-year Pain Reliever Use Disorder[a]													
12+	1546 (0.6)	1636 (0.7)	1715 (0.7)	1715 (0.7)	1878 (0.7)	1923 (0.8)	1768 (0.7)	2056 (0.8)	1879 (0.7)	1918 (0.7)	2038 (0.8)	1753 (0.7)	1678 (0.6)
12–17	275 (1.1)	265 (1.0)	238 (0.9)	254 (1.0)	218 (0.9)	238 (1.0)	250 (1.0)	150 (0.6)	134 (0.5)	168 (0.7)	122 (0.5)	152 (0.6)	99 (0.4)
18–25	541 (1.7)	485 (1.5)	559 (1.7)	580 (1.8)	565 (1.7)	609 (1.8)	580 (1.7)	649 (1.9)	485 (1.4)	430 (1.2)	427 (1.2)	291 (0.8)	339 (1.0)
26+	730 (0.4)	885 (0.5)	919 (0.5)	881 (0.5)	1095 (0.6)	1075 (0.6)	938 (0.5)	1258 (0.6)	1260 (0.6)	1320 (0.6)	1489 (0.7)	1310 (0.6)	1240 (0.6)

Data from: Center for Behavioral Health Statistics and Quality [58, 59]

[a]Because of changes to the NSDUH questions on misuse of prescription drugs, the 2015–2017 estimates for pain reliever use disorder are not comparable with estimates from earlier years

2000s [20, 67]. However, between 2005 and 2015, an increasing number of people entering addiction treatment report initiating opioids with heroin (from 8.7% in 2005 to 33.3% in 2015) [68]. Opioid use disorders due to opioid pain relievers and heroin are not mutually exclusive, and approximately 220,000 Americans met criteria for opioid use disorder related to both heroin and pharmaceutical opioids in 2017, which amounts to about 10% of people with an opioid use disorder in the past year [58].

Illicitly Manufactured Fentanyl Use

The increase in synthetic opioid-related deaths has been paralleled by a rise in the supply of high-potency illicitly manufactured fentanyl analogs in the street drug supply. In illicit drug markets, fentanyl and its analogs are being increasingly mixed with nonopioid drugs such as cocaine [69] as demonstrated by increasing rates of cocaine overdoses involving opioids [11]. Individuals who use drugs may not always be aware their drug supply contains fentanyl [70]. Given the recency of illicitly manufactured fentanyl in the drug markets, national surveys do not yet capture known or intentional use of fentanyl.

Social, Political, and Economic Factors

Political, social, and economic factors have likely played an important role in the evolution of the opioid overdose epidemic [17]. Homelessness, unemployment, and receipt of social welfare have been associated with overdose [71–74]. In qualitative studies, factors such as financial pressure and limited housing may contribute to overdose risk-taking behavior as a "way out" [75, 76]. Green and colleagues hypothesized that structural factors may explain part of the relationship between HIV and overdose [77]. Further studies have shown that concerns about stigma, housing insecurity, and fear of police may adversely impact effective responses to overdose by witnesses [78, 79]. Addressing the opioid overdose epidemic clearly requires policies and interventions that adopt a more holistic approach beyond addressing known drivers of the epidemic, such as prescribing and the illicit drug trade.

Individual-Level Risk and Protective Factors for Opioid Overdose

Epidemiological data on the risk factors for opioid overdose are diverse and complex. Over the last four decades, opioid use patterns have shifted from heroin to pharmaceutical opioids, back to heroin, and, more recently, to illicitly manufactured fentanyl [17, 80]. In parallel with these use patterns, epidemiological studies on overdose have been conducted with the following data sources, populations, and settings:

1. Population vital statistics, including deaths identified from medical examiner records [81–87]
2. Postmortem samples [88–92]

3. Substance use disorder treatment programs, such as methadone programs [93–98]
4. Community-based outreach to recruit individuals who inject drugs and/or use heroin, such as from syringe service and other harm reduction programs [72, 73, 76, 99–102]
5. Populations with criminal justice involvement [103, 104]
6. Patient cohorts (e.g., patients prescribed chronic opioid therapy, pregnant and postpartum women, and individuals with a prior overdose) derived from health insurance plans and systems, such as the Veterans Administration, Medicaid, integrated health systems, and national registries [64, 105–111]
7. Pharmacologic studies and clinical trials [112]

Studies have defined overdose using a variety of approaches. Overdose outcomes have included fatal [82, 98, 113, 114] and/or nonfatal [72, 110, 115] overdose events attributed to prescribed pharmaceutical opioids, illicit pharmaceutical opioids, heroin, or illicitly manufactured fentanyl. Although overdose has been primarily defined as an unintentional (accidental) event [114], studies have also included events of undetermined intent [62, 116] and intentional (suicidal) events in their analyses [71, 117]. These heterogeneous definitions of opioid overdose outcomes render interpreting results across studies difficult [77], particularly since many overdose deaths involve multiple substances and identifying specific opioids in postmortem samples can be complex [118].

Once an overdose definition is in place, studies have used a variety of approaches to identify overdose events. Nonfatal overdoses may be reported via surveys [74, 93, 102, 119, 120] by individuals who either experienced or witnessed overdose events. Fatal overdoses may be identified from medical examiner records, vital statistics, and data linkages with a state or national death registry (e.g., the National Death Index [121]) [82, 107, 113, 122]. Overdoses that come to medical attention may be identified with International Classification of Diseases (ICD) codes that are extracted from electronic health records and medical claims [64, 105–108, 123]. Other approaches for identifying overdose include linking criminal justice records or data from convenience samples to national vital records [100, 122].

Correlates and risk factors for overdose have been identified by toxicology, survey, and electronic health record data. Each of these approaches has contrasting strengths and limitations. For example, surveys can be used to collect self-reported data on exposures and outcomes from populations that may not present to medical attention, such as uninsured and homeless populations. Self-report data, however, are subject to recall bias and survival bias if the information is collected after the overdose event has occurred. Although these biases can be mitigated by using a longitudinal design with prospective data collection, such studies tend to be time-consuming and resource intensive. In contrast, electronic health record and claims data are longitudinally captured medical encounter data and can be efficiently obtained from very large populations, without having to rely on participant recall. These data, however, are subject to missingness and measurement error and often lack detailed information on drug use behaviors.

Across these variable epidemiological designs, data sources, data collection methods, and outcome definitions, studies have identified four important, clinically relevant factors that influence overdose risk.

1. Opioid dose, potency, duration of action, tolerance, and route of administration
2. Polysubstance use and polypharmacy
3. Underlying psychiatric and medical comorbidities
4. Treatment medications

These findings will be discussed in greater detail in the subsequent sections.

Opioid Dose, Potency, Duration of Action, Tolerance, and Route of Administration

Prescription opioid dose and duration of action are strong risk factors for overdose, based on evidence from at least five large observational studies of patients prescribed chronic opioid therapy [62, 105, 107, 109, 124]. The studies on dose examined associations between MME and opioid-related fatal and/or nonfatal overdoses [105, 107, 109], adjusted for demographic and clinical characteristics. All analyses demonstrated a dose-response relationship between MME and overdose. The strongest association was found in the cohort study by Dunn et al., showing relative risks of 1.44, 3.73, and 8.87 across MME categories of 20–49, 50–99 and ≥100, respectively [107]. A large cohort study on the duration of action showed that patients in the Veterans Administration initiated on long-acting (LA) opioid formulations were at a greater than five-fold increased risk for overdose within the first 14 days following therapy initiation when compared to patients initiated on a short-acting formulation, controlling for demographics, concomitant medications, comorbidities, and opioid dose (MME) [124]. Based in part on these results, the CDC Guideline for Prescribing Opioids for Chronic Pain suggests clinicians reassess the risks and benefits of opioids when increasing doses above 50 MME, avoid doses above 90 MME, and avoid initiating patients on extended-release (ER) and LA opioid formulations [31].

The role of opioid dose and potency on opioid overdose risk been highlighted by an unprecedented increase in deaths attributed to illicitly manufactured fentanyl and its analogs, starting in 2014 [11]. Fentanyl was developed in 1960 and is known to have high analgesic potency [125, 126]. It is frequently used clinically as a transdermal patch, which provides continuous dosing while the patch is worn [125]. However, it has more recently been illicitly manufactured, with a higher potency than morphine [69, 127]. This makes it easier to transport and avoid detection. Other fentanyl derivatives, such as carfentanil, also known as “elephant tranquilizers,” may be many times more potent than morphine [126]. Due to their potency and the unpredictability of their presence in the street drug supply, illicitly manufactured fentanyl and its derivatives are therefore responsible for exponential increases in overdose deaths [128].

The euphoric and respiratory depressant effects of opioids act on different regions of the brain, and it has been suggested that tolerance to the respiratory effects lags behind tolerance to euphoric effects of opioids [129]. Thus, loss of tolerance has long been considered a risk factor for opioid overdose [130, 131], which may partially explain elevated risks of overdose after prolonged periods of abstinence [132]. For example, studies have demonstrated greater than threefold increased risks for overdose in the first 1–2 weeks after release from prison relative to subsequent periods at risk in the community [104, 133]. Similarly, the first 4 weeks after the end of pharmacologic treatment for opioid use disorders has been associated with a greater than eightfold increased risk for overdose relative to the time on treatment [134]. Given that tolerance is influenced by learning, these post-prison and posttreatment effects are also supported by early research showing that the tolerance effects of opioids are affected by changes in the environments in which the opioids are ingested [135, 136].

Absorption across different routes of administration varies across pharmaceutical and illicit opioids [137]. For heroin, that has limited oral absorption, injection drug use may be associated with an increased overdose risk relative to other forms of administration, such as smoking [1, 93].

Polysubstance Use and Polypharmacy

Although opioid dose is an established risk factor for overdose, the term "overdose" to describe acute toxicity from opioids may be misleading because it only implies that an individual took a high enough amount of the substance to elicit potentially fatal sequelae [138]. Early studies of opioid overdose, however, demonstrated that blood concentrations of heroin metabolites (morphine) among individuals who died were not significantly higher than among individuals who did not die [139]. It is extremely common for heroin overdose victims to have one or more potentially toxic substances in their blood or urine, such as ethanol, benzodiazepines, cocaine, and methamphetamine [86, 88, 92, 138]. For instance, in a Norwegian study of 1474 forensic autopsy cases positive for a heroin metabolite, 21% had at least ethanol detected, and 84% involved another substance, such as benzodiazepines, amphetamines, and cannabis [92]. In the United States, reporting of specific substances on death certificates has improved over time [86]. By 2014, at least one concomitant drug was mentioned in 51.6%, 76.2%, and 80.4% of deaths attributed to heroin, oxycodone, and hydrocodone, respectively [86]. Below, we discuss the three most common classes of cooccurring substances in opioid-related overdoses—benzodiazepines, alcohol, and stimulants.

Benzodiazepines

Benzodiazepines are the most commonly identified substances in pharmaceutical opioid overdose deaths [86, 107, 109, 113, 140]. Benzodiazepines are sedative hypnotics that act via the γ-aminobutyric acid type A ($GABA_A$) receptor, producing relatively weak respiratory depressive effects when ingested on their own [129, 141].

Concurrent prescribing of benzodiazepines and opioids increased significantly from 2002 to 2014 [142, 143], while deaths involving benzodiazepines increased more than four-fold over the same time period [11]. Although benzodiazepines alone are generally believed to be associated with a low risk for overdose, an ecologic analysis of county-level prescription and overdose data demonstrated a possible synergistic association between opioids and benzodiazepines and overdose mortality [144].

Observational studies using individual-level data have shown that concurrent use of benzodiazepines and opioids magnifies the sedating and respiratory depressive effects of the latter drug [64, 106, 107]. Among individuals prescribed opioids for pain, studies have found statistically significant associations between benzodiazepine prescribing and overdose [64, 106, 107, 109, 111, 145]. For example, in a case-cohort study of US veterans receiving opioid therapy, Park and colleagues showed a dose-dependent association between benzodiazepine prescribing and drug overdose. As the daily benzodiazepine dose increased from 11 to 20 mg to more than 40 mg, the relative risk of overdose increased from approximately 1.7 to 3.0 when compared to patients receiving ≤10 mg [64].

Studies examining the association between benzodiazepine and opioid co-prescribing have tended to use electronic health record, pharmacy, medical claims, and various sources of cause of death data to identify large populations of patients receiving opioid and benzodiazepine therapy. Overdose outcomes in these studies were ascertained based on ICD-9/ICD-10 diagnosis codes (International Classification of Diseases, 9th and 10th revisions) recorded in healthcare encounters and on death certificates [64, 106, 107]. Data were also collected to assess demographic factors and control for potential confounding factors, such as mental health disorders, comorbidities, and substance use disorders [64, 106, 107]. Controlling for such variables is important because patients indicated for concurrent prescribing of benzodiazepines and opioids may also have demographic, behavioral, and clinical characteristics independently associated with intentional (suicidal) and unintentional overdose death.

The case-cohort study by Park and colleagues (2015) produced results suggesting an interaction between the type of benzodiazepine and drug overdose risk. For instance, in combination with opioids, temazepam was associated with lower risk of drug overdose compared to clonazepam [64]. Future studies should continue to rigorously explore potential differences in risk across various benzodiazepines, as these drugs have heterogeneous pharmacokinetic and pharmacodynamic profiles, leading to diverse potential drug-drug interactions among different benzodiazepines and opioid medications [141]. Further work should also be done to identify clinical scenarios and dosing regimens that are low risk or in which the benefits of treatment outweigh the risks [146].

Alcohol

It is generally believed that alcohol potentiates the risk of opioid-induced respiratory depression. Since the 1980s, several international studies have shown that ethanol is commonly present in postmortem toxicological blood and urine analyses from deaths attributed to heroin [89–92, 147]. Ethanol likely influences the metabolism

of heroin by inhibiting the hydrolysis of 6-acetylmorphine (6-MAM) to morphine. Studies have shown that morphine/6-MAM ratios in overdose autopsy cases are significantly lower in ethanol positive than ethanol negative cases. Since 6-MAM binds opioid receptors with a greater affinity than heroin itself [148], the increased presence of 6-MAM may elevate the risk of overdose [92]. Due to lower tolerance, intermittent heroin use in the setting of heavy alcohol use may also be a risk factor for overdose [91].

For pharmaceutical opioids, ethanol likely increases the risk for opioid-induced respiratory depression, albeit through different biological mechanisms which have not yet been elucidated. Approximately one in five opioid pain reliever related deaths involves ethanol [85, 113]. In a clinical study of oxycodone and ethanol, the combination of 20 mg immediate release oxycodone with ethanol was associated with apneic events and oxygen desaturation [112]. Potential mechanisms include increased oxycodone concentrations and mu receptor sensitization [112].

Stimulants

Cocaine and methamphetamine are commonly used with heroin and commonly identified in overdose events [18, 74, 82, 93, 98, 100]. Animal studies suggest increased reward from the use of heroin and cocaine [147]. In 2016, cocaine was mentioned in 20.0% and methamphetamine in 6.7% of heroin-related overdose deaths [86].

Having a combined opioid use disorder and cocaine use disorder is associated with an increased risk of death relative to a cocaine use disorder alone [94]. Although cross-sectional survey studies suggest injecting cocaine or methamphetamine with heroin may be correlated with self-reported overdose [149, 150], the risk of overdose mortality following injecting both stimulants and heroin has not been established. Moreover, unlike alcohol and benzodiazepines, cocaine and methamphetamine are stimulants with no known respiratory depressant effects.

Underlying Psychiatric and Medical Comorbidities

Psychiatric comorbidity has frequently been cited as a risk factor for overdose. In various study populations, histories of depression, panic disorders, or other anxiety disorders were positively associated with overdose [105, 107, 108, 120, 123, 151–153]. Being prescribed a psychiatric medication during imprisonment has been associated with overdose after release from prison [151] and a history of psychiatric treatment and prior suicide attempts have been associated with repeat drug overdose events [71]. However, it is not clear if psychiatric disorders are independent risk factors for opioid overdose given that they are highly correlated with other known risk factors, such as receipt of other sedating medications (e.g., benzodiazepines). Further, suicides may be misclassified as unintentional or undetermined overdose events [154].

It is biologically plausible that certain medical comorbidities, such as underlying pulmonary disease, respiratory infections, liver disease, HIV, and obstructive sleep

apnea, could increase the risk for opioid overdose [77, 130, 155]. A meta-analysis identified a positive association between HIV infection and overdose [77]. Other epidemiological studies have identified positive associations between medical comorbidities and opioid overdose risk [152, 155], while one case-cohort study of US veterans identified a protective effect of chronic obstructive pulmonary disease, cardiovascular disease, and sleep apnea on pharmaceutical opioid overdose risk [105]. Given these conflicting findings, studies specifically evaluating the role of medical comorbidity in opioid overdose are needed.

Treatment Medications

Treatment with methadone and buprenorphine, opioid agonists, is generally associated with reduced opioid overdose mortality [110, 134, 156, 157]. Based on a systematic review and meta-analysis of observational studies of individuals with opioid use disorder, the estimated rate of overdose death off methadone treatment was nearly fivefold higher than on the treatment [157]. For buprenorphine, the overdose mortality rate was more than threefold higher off treatment than on treatment (4.6 vs 1.4 overdose deaths per 1000 individuals) [157]. Retention in treatment more than 12 months is also associated with a reduction in overdose risk [134, 156]. However, the first 4 weeks on treatment and the first 4 weeks after discontinuing treatment represent periods of high risk, relative to the rest of time on treatment or after discontinuing treatment, respectively [134, 157]. A Swedish cohort study conducted a self-controlled analysis in which time periods within treated individuals were compared. The analysis identified a reduction in overdose risk for periods on buprenorphine or naltrexone (opioid antagonist) treatment and small increased risk of overdose during periods on methadone, despite improvements in other outcomes such as suicidal behavior and arrests [158]. A retrospective cohort study in the US state of Massachusetts conducted between 2012 and 2014 found that treatments with methadone or buprenorphine after a nonfatal overdose were each associated with decreased all-cause and opioid-related mortality. Among individuals who experienced a nonfatal overdose, methadone treatment was associated with a 53% decrease in all-cause mortality and a 59% decrease in opioid-related mortality relative to no treatment, while buprenorphine was associated with a 37% and 38% decrease in all-cause and opioid-related mortality, respectively. Treatment with the opioid antagonist, naltrexone, was not associated with mortality benefits [110].

Studies with people who have criminal justice involvement suggest that treatment with opioid agonists in prison is associated with significant reductions in post-release drug overdose death rates [159]. Exposure to non-pharmacologically based substance use disorder treatment is also associated with reduced overdose mortality [103].

Naloxone is an efficacious opioid antidote that reverses respiratory depression due to opioid poisoning (overdose). Naloxone has traditionally been administered by medical personnel in emergency settings and hospitals. Since 1996, community-based organizations in many states have implemented overdose education and naloxone distribution programs for people who use heroin and illicit pharmaceutical

opioids [102, 160]. These programs educate people who use drugs and dispense naloxone "kits" for take-home use, so that naloxone may be administered by a lay bystander during an overdose. Evaluations of these community programs suggest that naloxone can be administered by nonmedical bystanders to prevent deaths from overdose [102, 160–162]. Early naloxone administration, while awaiting the arrival of emergency medical services, results in faster resumption of respiration, thus preventing brain anoxia, medical complications, and death [163]. Internationally, prison-based naloxone programs have also shown favorable preliminary outcomes to reduce post-release overdose mortality [164]. Thus, expanding access to naloxone is one strategy to reduce the risk of opioid overdose fatalities.

Conclusions and Implications for Prevention

Opioid overdose is the most serious complication of opioid use and opioid use disorder. The US opioid overdose epidemic has been driven by opioid prescribing trends and illicit drug markets for heroin and fentanyl as well as diverted opioid pain relievers. These ecologic trends suggest a complex and worsening public health problem that requires a multifaceted response. For instance, trends in medical complications of opioid use such as infectious diseases suggest vaccinations, infectious disease screening and treatment, policy, and behavioral interventions are needed. Risk factors for overdose include increasing opioid dose and potency, loss of tolerance, polysubstance use and polypharmacy, and underlying psychiatric and medical comorbidities. In addition, they indicate that overdose can be effectively prevented with opioid agonist treatment and reversed with naloxone. Together, these epidemiologic findings suggest clinical and policy initiatives are needed to expand access to pharmacotherapy and increase availability of the overdose reversal agent naloxone.

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Neurobiology of Addiction: A Disorder of Choice

3

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Introduction

In the *Diagnostic and Statistical Manual of Mental Disorders*, 5th Edition (DSM-5), the clinical entity of substance use disorder (SUD) has 11 clinical criteria, with a severity score assigned based on the number of criteria met [1]. As noted in Table 3.1, these criteria may be broken up into three clusters corresponding to three clinical domains: (a) physical dependence, including the related phenomena of tolerance and withdrawal that arise from physiological adaptation in the presence of the addictive substance; (b) signs of outward harm, such as damaging effects on relationships and life roles; and (c) a cluster of criteria that speak to the behavioral state of *compulsion*—ongoing use despite the intention to stop and despite negative consequences of which the individual is aware, often driven by subjective cravings. It is this compulsion cluster that is at core of the clinical state of *addiction*, which we will define, for the purposes of this chapter, as severe SUD—i.e., SUD with six or more DSM-5 criteria met. In order to qualify for severe SUD, a patient must meet at least one criterion from the compulsion cluster. Moreover, the clinical phenomena in that cluster often reflect the deepest problems faced by clinicians and patients affected by SUD. Indeed, the behavioral state of compulsive drug use is often perplexing to clinicians—as well as patients themselves and their loved ones—in that affected patients continue to make the decision to use a substance that ultimately results in profound drug-related morbidity, along a broad spectrum that ranges from

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Table 3.1 The DSM-V definition of substance use disorder (SUD), broken up into three clusters of criteria

Cluster	SUD criteria
Physical dependence	Tolerance Withdrawal
Signs of outward harm	Use in hazardous situations Social/interpersonal problems related to using Major roles neglected in order to use
Compulsion to use	Use of larger amounts of a substance or for longer than intended Repeated attempts to quit or control use of a substance Excessive time spent in using Use despite known physical/psychological problems related to use Activities given up due to use Craving to use a substance

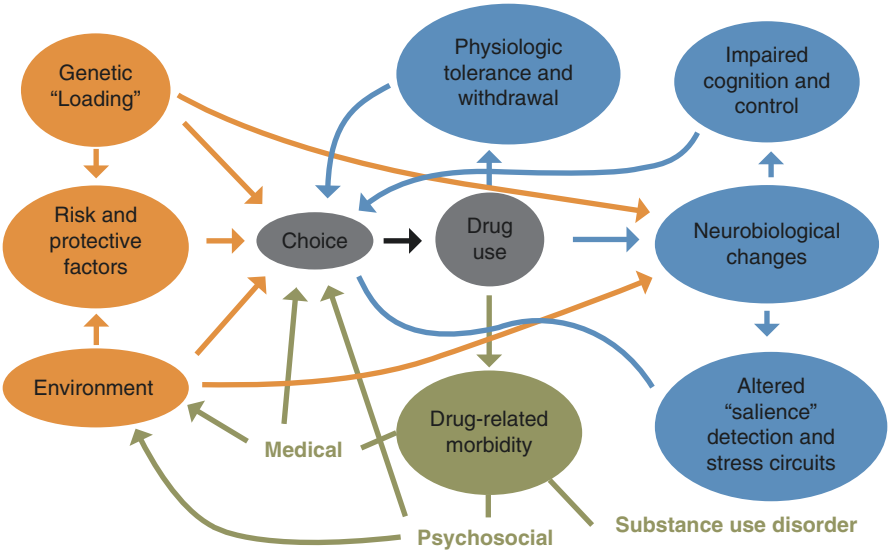

Fig. 3.1 Framework for addiction as a disorder of choice

acute to subacute to chronic medical and psychosocial conditions. Why would a patient continue to "choose" to use a substance that is causing so much harm in so many ways?

The answer lies in the concept that addiction is in essence a neurobiological disorder of choice in which decision-making becomes more and more heavily weighted in favor of using an addictive substance (Fig. 3.1). This weighting includes inherited and environmental factors that can set up conditions that differentially predispose individuals to different initial experiences of using the drug that can be aversive, neutral, or enjoyable, potentially biasing toward repeated use; physiological adaptations to the presence of the drug in the body that cause tolerance and

withdrawal; and the effects of drug-related morbidities themselves, which can feed back and affect the conditions experienced by the affected individual (such as the person's living environment or physical conditions such as chronic pain). At the same time, a deeper weighting process plays out in the brain of the affected individual, involving a series of neurobiological changes that affect decision-making—and it is these neurobiological changes that are the primary focus of this chapter.

The neurobiological changes affecting decision-making that occur with exposure to addictive substances can be put into two categories. First, changes occur in two "bottom-up" brain systems that operate automatically to (a) detect what is important and rewarding (or salient) in the environment and direct motivated behavior in favor of those stimuli, and (b) shape behavior based on stressful stimuli and aversive internal states. These symptoms are sometimes referred to as an "impulsive system" for the automatic, habitual pursuit of advantageous behaviors [2]. Second, changes occur in the "top-down" brain system that considers options, makes predictions, and controls automatic behaviors—a system sometimes referred to as a "reflective system" necessary for careful decision-making [2]. In each of these systems (salience detection, stress reactivity, and cognitive control), changes occur at three levels: molecules (neurotransmitters, neurotransmitter receptors, and signaling proteins), cells (neurons, their input and output communication elements known as dendrites and axons, respectively, and support cells known as glial and microglial cells), and ultimately networks of neurons that process information and accomplish decision-making tasks. The primary areas of the brain involved in these networks are shown in Fig. 3.2. Salience detection primarily involves communication between the ventral tegmental area (VTA) in the midbrain, the ventral striatum (part of the basal ganglia), and the prefrontal cortex (PFC), with further connections between the striatum and motor

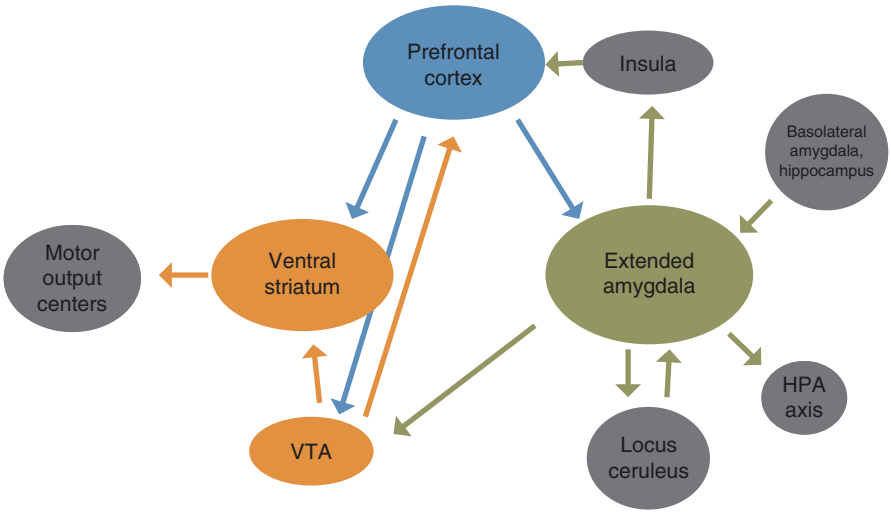

Fig. 3.2 Areas of the brain involved in three key neurobiological processes that affect decision-making: salience detection *(in orange)*, stress processing *(in green)*, and cognitive control *(in blue)*

output centers that enact motivated behavior. Stress processing is centered in a collection of nuclei known as the extended amygdala, which communicates with the salience detection and cognitive control systems, areas in the midbrain and hypothalamus that elicit physical stress responses (e.g., through the hypothalamus-pituitary-adrenal or HPA axis), memory areas (such as the hippocampus), and the part of the brain responsible for reading internal states (the insula). Cognitive control depends on areas in the prefrontal cortex and their top-down connections with the salience and stress systems. In this chapter, we will first focus on these three primary neurobiological systems one by one, discussing some of the molecular, cellular, and network changes that occur in these interacting decision-making circuits. Then, we will focus on the neurobiology of opioid use disorder (OUD) as a specific example of how the brain's decision-making machinery can be powerfully influenced by an addictive substance at many levels. Finally, we will show how lessons learned from the study of addiction neurobiology may provide a framework for designing novel treatments for SUD, both pharmacologic and nonpharmacologic.

A few further notes before we begin. First, a number of experimental animal models—both in rodents (rats, mice) and nonhuman primates—have been developed over the past four decades to try to unravel the neurobiological changes that give rise to addiction [3]. These experimental protocols can be divided into two types. In "non-contingent" protocols, the experimenter delivers a drug and observes downstream behavioral effects, such as locomotor sensitization (stereotyped repetitive behaviors elicited by a stimulant), classical conditioning (in which the animal learns an association between the drug reward and a conditioned stimulus) or conditioned place preference (learning to prefer one location over another). In "contingent" protocols, the animal is allowed to develop a pattern of self-administration of an addictive substance, and the experimenter observes downstream effects, such as behavior during withdrawal from the substance and reinstatement of drug seeking by cues or by stress; these latter types of experiments are felt to have more validity as a proxy for addictive behavior in humans [4]. More detailed neurobiological investigation has been done in these experimental models using anatomical studies, molecular biological methods, and electrophysiological recordings from neurons and brain slices. More recently, neurobiological mechanisms have been dissected using optogenetic techniques, which involve the use of light-sensitive proteins that can turn on or off the electrical excitability of well-defined neuronal populations in awake, behaving animals [5, 6].

Second, studies of the neurobiology of choice in human subjects have been accomplished primarily using functional neuroimaging—positron emission tomography (PET) scanning and functional magnetic resonance imaging (MRI) [7, 8]. PET scanning involves using a radio-labeled compound (such as a neurotransmitter, a receptor ligand, or glucose) to map brain activity; functional MRI involves using the differential magnetic properties of oxygen-poor and oxygen-rich hemoglobin to map brain metabolism. These methods have been used in drug-naïve subjects as well as in patients with established SUD, and protocols have included challenging subjects with a drug or drug-related cues/imagery or scanning patients at various stages of addiction and recovery to examine time-dependent changes. Neuroimaging has often been done alongside behavioral reports (e.g., of the euphoria experienced

after a drug ingestion or of craving or other affective symptoms during drug abstinence) or tests of cognition and decision-making, such as memory/attention testing or the Iowa Gambling Task, which assesses the ability to sustain short-term losses to win future gains [2].

Finally, there are those who feel that too much emphasis on SUD as a "brain disease" is unhelpful. The concern is that an exclusive focus on brain mechanisms may over-medicalize SUD—obscuring the truth that recovery is a "project of heart and mind"—and oversells what we know about the relationship between brain function, human decision-making, and human behavior—i.e., the relationship between brain and the emergent properties of mind and person. In positing that the neurobiological machinery of choice has been "hijacked," there is a danger of underrecognizing the power that people affected by SUD retain over their behavior and neglecting the other factors (such as family systems, spirituality, social and economic contingencies and consequences, or other determinants) that can powerfully affect addiction and recovery in ways that may not be as prominent in other medical or psychiatric disorders [9]. Moreover, use of the term "disease" may imply more mechanistic understanding of addiction than science can currently offer [9, 10]. That being said, thinking of SUD as a chronic, relapsing brain disease—as has been promoted forcefully by the National Institute on Drug Abuse (NIDA) since the 1990s by directors Alan Leshner, Nora Volkow, and others—has been an important part of fighting stigma against patients affected by addiction and arguing effectively for parity with other disorders in recognition and research funding [9–11]. In addition, understanding the neurobiology of addiction expands the toolbox of clinicians, helping organize and categorize the clinical phenomena seen every day in the clinic and providing a useful framework to find new therapeutic targets [12]. In the end, the most useful way to think of SUD may be as a disorder of choice—a clinical syndrome in which the brain's ability to choose becomes disordered through a complex pathophysiology—not yet fully understood—involving neurobiological changes that often occur alongside and in concert with many other complex, interacting layers of emotional, social, and societal pathology.

Changes in Salience Detection

The first set of neurobiological changes we will consider involve the neural circuits that detect in the environment what is rewarding or important for survival—a concept defined as "salience." The salience of an event or stimulus is driven either by its unexpectedness, its reinforcing effects (either positive or negative), or its conditioned expectation of association with an important stimulus. In the human brain, the primary signal for salience is the modulatory amine neurotransmitter dopamine, which is distributed by midbrain neurons to various areas in the forebrain and causes modifications (plasticity) in brain circuits that modulate motivated behavior toward pursuit of the salient stimulus. It is currently believed that addictive drugs are reinforcing not necessarily because they are pleasurable or rewarding (although they often are, especially with initial use) but because they all, via various direct or

indirect mechanisms, promote dopamine signaling by midbrain neurons. By triggering the release of dopamine, drugs of abuse falsely proclaim themselves to the brain as salient stimuli, equal in importance to natural stimuli relevant for survival such as food, water, or sex. In fact, as we will discuss further below, the dopamine signals produced by addictive substances are stronger than those produced by natural stimuli, exaggerating the brain's estimate of their salience and accelerating brain changes that bias behavior toward seeking of the drug.

Key Systems

The parts of the brain involved in salience detection are shown in Fig. 3.3 and make up what is known as the "mesocorticolimbic dopaminergic system." The key connection in this system is a projection of dopamine from neurons in the Ventral Tegmental Area (VTA) in the midbrain to the ventral striatum, a nucleus deep in the forebrain that plays an important role in directing motivated behavior based on salience. The ventral striatum projects to other brain nuclei (such as the ventral pallidum and thalamus) that help gate motor activity and are modulated by the cognitive centers of the prefrontal cortex—which itself receives a projection of dopamine from the VTA. Stress-related nuclei of the extended amygdala project to the VTA and modulate the salience detection system.

Neurobiological Changes

How does dopamine signal salience in the ventral striatum? Dopamine's most important role may be to signal "reward prediction errors" (RPEs), which contribute to long-term associative learning. In the brain's natural state, dopaminergic neurons in the VTA respond to natural rewards such as food with a burst release of dopamine into the ventral striatum and other areas. Notably, there is baseline (tonic) electrical "firing" of dopaminergic cells in the VTA (at a frequency of 1–8 per second) which

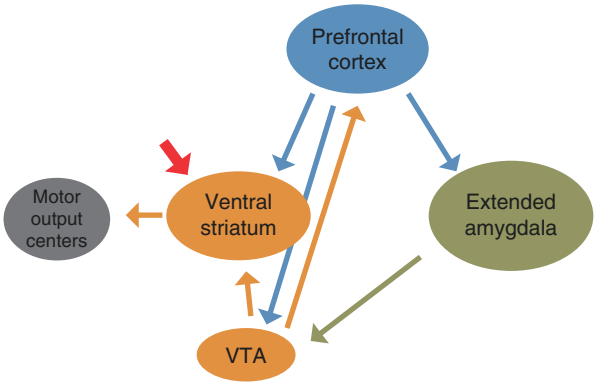

Fig. 3.3 Areas of the brain involved in salience detection

is associated with baseline motivational drive. However, certain environmental stimuli have the capability to temporarily activate burst (phasic) firing of dopamine cells (at a higher rate of 15 per second), which serves as the true salience signal above and beyond this baseline activity [13]. Through associative learning, environmental cues that are temporally correlated with the rewarding stimulus can also take on the ability to evoke a burst dopamine signal, and there is a gradual shift to a state in which the temporally correlated cue evokes the burst, but not the original stimulus itself. The magnitude of dopamine released in response to these conditioned cues is inversely proportional to the degree to which the associated reward was expected—i.e., rewards which are unexpected produce a much stronger burst than rewards which are expected, and when a reward fails to materialize after an associated cue, baseline dopamine signaling decreases [14]. This finding is significant because it suggests that burst dopamine signaling does not occur in a static or all-or-none fashion to salient stimuli and environmental cues. Rather, dopamine neurons adapt their firing response downward as previously novel stimuli and cues become more familiar, such that the dopamine signal is oriented primarily toward novel salient stimuli and associated cues. The critical function of the dopamine signal, therefore, may be in allowing an organism to identify novel environmental cues that are likely to predict a reward and, if that prediction is ultimately correct, to encode that information to influence future behavior [15]. Notably, there are multiple cell populations within the VTA other than the primary dopaminergic neurons that receive synaptic input from multiple other brain regions and interact with each other prior to dopamine cell firing, underscoring the upstream processing that occurs before a dopamine signal is generated [16, 17]. Associative learning that pairs conditioned environmental cues with drug stimuli and allows for cue-related dopamine signaling (and, as will be explained below, cue-related cravings and relapse) may be mediated by inputs from the amygdala, hippocampus, prefrontal cortex, and medial thalamus [11, 18].

How do addictive substances take over this salience-detection system? All known addictive substances cause an exaggerated dopamine salience signal in the ventral striatum, although the ways in which that occurs are diverse [19] (see Table 3.1). For example, stimulants, such as cocaine and amphetamines, directly enhance dopaminergic signaling through mechanisms such as decreased reuptake after release from synaptic terminals, or a combination of decreased reuptake and increased synaptic release. In contrast, opioids are thought to increase dopaminergic signaling by reducing the inhibitory action of neurons expressing the neurotransmitter GABA (gamma-aminobutyric acid) on dopamine-producing neurons in the VTA. The critical difference between dopamine release in response to a natural reward (such as food) and an addictive substance is that food (and eventually a food-related cue such as its sight or smell) elicits a moderately sized, transient surge of dopamine that progressively diminishes as the reward becomes more expected, whereas the addictive substance triggers a larger release of dopamine—determined by the pharmacologic properties of the drug itself—that can become associated with a cue but is not modulated by reward expectation and does not attenuate over time [15]. In essence, addictive substances mimic an RPE predicting a highly novel stimulus every time they are

self-administered, thereby powerfully invoking the associative learning function of the dopaminergic salience signal [20, 21]. Repeated use of an addictive substance generates a flood of dopamine release into the synapse that is interpreted by the brain, via the RPE mechanism, to represent an unexpected reward, even though it is a pharmacologic event that occurs independently of the upstream processing that occurs for natural stimuli. In other words, addictive substances uncouple the relationship between the dopamine signal and the degree to which a cue-associated reward was expected. Long after a person who uses drugs has ceased to experience the drug and its associated physiologic reward as novel, the magnitude of the dopamine released triggered by drug-related cues will remain relatively undiminished, fixed by the properties of the drug itself. And this misinterpretation of pharmacology for neurobiological processing results in a spiral of associative learning in which drug-related cues become reinforced to pathological levels, surpassing the value of natural rewards and cues associated with them. As a result, when given the choice between an addictive drug and a natural reward, the brain may develop a behavioral bias toward the drug that strengthens with each successive use—a phenomenon that can help explain some of the most challenging behavioral aspects of addiction, such as progressive allocation of disproportionate time and resources to obtaining addictive substances or persistent use of those substances at the expense of natural rewards and in spite of negative consequences [11, 15, 22, 23]. For a person with a substance use disorder, the common self-described experience of the drug as feeling "better than food, "better than sex," or more important to the individual than responsibilities such as working, paying rent, or caring for family members may in fact be deeply rooted in this complex neurobiological pathophysiology.

How does the dopamine signal from VTA to ventral striatum encode information? The actions of dopamine from the VTA center on a specific population of striatal neurons known as medium spiny neurons (MSNs) that contain the neurotransmitter GABA. These neurons are prolific integrators of information, each receiving thousands of stimulatory glutamatergic inputs from cortical and limbic regions and providing output to downstream motor centers of the brain, such as the globus pallidus [24]. The glutamatergic inputs to MSNs are modulated by dopamine and likely play an important role in motivated drug seeking, given that microinjection of glutamate receptor blockers into the ventral striatum of stimulant-dependent experimental animals can prevent reinstatement of drug use after a period of abstinence [19]. Through downstream molecular signaling pathways and changes in gene expression, dopamine modulation of MSNs may alter the types and distribution of glutamate receptors on MSN dendrites (input elements), causing a long-lasting change in synaptic function known as long-term depression (LTD), a mechanism involved in learning and memory throughout the brain. This change in the efficacy of glutamatergic input may then affect downstream signaling from the ventral striatum to motor output centers, with effects on the regulation of motivated behavior, and may underlie a loss of sensitivity of ventral striatal neurons to natural rewarding stimuli after a period of persistent drug use [25]. A further long-lasting change in the types of glutamate receptors on MSNs that occurs during prolonged abstinence after a period of use—which can be reversed quickly upon drug re-exposure—may also explain the

experimental phenomenon of "incubation," in which drug craving and drug seeking increase progressively over the first few months after withdrawal from a period of drug use [26]. Of note, as habitual drug use becomes more behaviorally hardened, signaling may shift from the ventral striatum to the dorsal striatum, which governs more automatic behaviors rather than behaviors driven by reward prediction [11]. Also of note, changes in synaptic strength also occur upstream of striatal MSNs, at the level of the VTA, where excitatory glutamatergic input to dopaminergic neurons increases with exposure to addictive substances, driven by an alteration in the ratio of different types of glutamate receptors on those neurons; in part, these changes are caused by a positive feedback loop in which modulatory neurons in the ventral striatum project back to the VTA and disinhibit dopaminergic neurons there [16, 19].

In addition to causing functional changes, dopamine effects on molecular signaling and gene expression in ventral striatum MSNs also cause long-lasting changes in the branching (arborization) of MSN dendrites and in the number of dendritic spines (synaptic input locations) on dendrites—structural synaptic changes that may encode drug-induced changes in motivated behavior [27]. Interestingly, while stimulants (amphetamine, cocaine, and nicotine) cause a long-lasting increase in dendritic arborization and spine density, ethanol and morphine cause a long-lasting decrease in those properties [24]. For all addictive drugs studied thus far in animal models, the structural changes remain long after discontinuation of the drug and are longer-lasting after self-administration than after non-contingent administration of an addictive drug [16, 19].

At the molecular level, the signaling pathway set off by dopamine binding to dopamine receptors that gives rise to the above functional and structural changes involves coupling of the receptor to a signaling protein called a G-protein, leading to upregulation of the intracellular messenger molecule cyclic AMP (cAMP). cAMP evokes a downstream cascade that culminates in production of the transcriptional regulator CREB (cAMP-response element binding protein) and a class of transcriptional regulators known as FOS-related antigens (FRAs), such as the molecule delta-FOSB—a molecule that can persist and affect gene expression patterns for weeks to months following drug exposure. These long-lasting molecules—conserved across species and shown to promote addictive behavior when "knocked in" genetically or artificially activated in ventral striatal cells in animal experiments—may represent a basic type of molecular "epigenetic switch," or molecular memory affecting gene expression, that lies at the root of the transition into the addicted state [11, 28–30]. Another type of epigenetic mechanism that contributes to molecular memory in addiction is modification of chromatin (larger-scale DNA winding structures), which allows differential gene expression in response to environmental stimuli; this type of molecular memory may explain the observation that nicotine pre-exposure enhances gene expression changes by cocaine [31].

Effects of addictive substances on the salience detection system have been shown in human subjects using functional neuroimaging methods. In fMRI studies, individuals with long-term cocaine use showed, at baseline, a reduction in dopamine release in the striatum and a reduction in the density of striatal dopamine receptors. These findings represent neural adaptations to chronic drug exposure that were overcome by

experimental methylphenidate injection and might be successfully overcome by use of increasingly larger doses of addictive substances, but not by natural environmental stimuli; this may explain a shaping of behavior toward drug stimulation and away from natural stimuli [32]. PET studies coupled with behavioral questionnaires have shown that a decrease in striatal dopamine receptors in subjects with severe alcohol use disorder is associated with decreased metabolic activity in the cognitive centers of the prefrontal cortex as well as an increase in alcohol craving severity and in cue-induced activation of frontal cortical regions. In addition, PET studies of patients with cocaine use disorder showed increases in striatal dopamine in the setting of cocaine-related video cues and cue-associated craving symptoms [8, 32, 33].

Behavioral Effects

Behavioral evidence of altered salience detection has been well defined in experimental animal symptoms. Conditioned place preference is an experimental protocol used to examine the development of an association between drugs and environmental cues, in which an experimental animal is given drug injections in one chamber of an experimental cage and is given control injections in an adjacent but contextually distinct chamber. The relative preference of the rodent for one chamber over another is subsequently assessed in a test session in which the rodent can freely choose to access either chamber in a drug-free state. In this protocol, the primary motivational properties of the drug serve as an unconditioned stimulus that is repeatedly paired with a previously neutral set of environmental stimuli that acquire, during the course of conditioning, secondary motivational properties such that they can later act as conditioned stimuli that create motivation [34]. The separate experimental phenomenon of behavioral sensitization refers to an increase in the behavioral effect of a drug that occurs as a consequence of past drug administration—a type of feed-forward phenomenon that is dependent on dopamine signaling in the ventral striatum, can happen with a number of different behavioral responses, and can persist for a long period of time after discontinuation of drug treatment. Animal models involving self-administration of drug—one step closer to the clinical scenario in humans—give powerful evidence of altered salience detection, including a preference for drug over natural stimuli including food or sex, use despite adverse conditions, and a ready resumption of self-administration after a period of abstinence provoked by presentation of the drug or a conditioned stimulus [35].

These findings in animal systems echo many of the clinical phenomena seen in the genesis of severe SUD in humans. Initial recreational or circumstantial drug use can transition over time to compulsive and often increasingly narrow or stereotyped patterns of drug seeking and drug-taking behavior via changes that resemble the experimental processes of conditioned place preference and behavioral sensitization. Due to the outsized dopaminergic response associated with drug-seeking behavior, this behavior often largely replaces goal-directed behavior toward stimuli that are necessary for survival or away from behaviors that pose serious risks. Moreover, the world of a patient with severe SUD is filled with conditioned stimuli of many kinds (i.e., the

places, people, or objects associated with the ritual of drug use) that can quickly trigger a dopaminergic burst and resumption of drug use after a period of abstinence. Neuroimaging studies confirm that the neural substrate for salience detection in rodent models is also found in humans and is active during the presentation of drug stimuli or conditioned stimuli [36, 37]. And ethnographic studies of patients suffering from severe SUD demonstrate that obtaining the resources to continue drug use becomes a major driving force that can dominate daily life and create a constant need to work or hustle [38].

Changes in Stress Signaling

The changes in the brain's salience detection system mentioned above provide an explanation for how addictive substances can take on (and in many cases, supersede) the positively reinforcing properties of natural survival-relevant stimuli. But many have argued that a complete description of the genesis of SUD cannot rely on positive reinforcement alone—that a "dark side" of negative reinforcement plays an equally important role in promoting and stabilizing the addicted state [4, 35]. This concept has its root in the theory of the "opponent process" originally put forward by Solomon and Corbit in the 1970s, in which a rapidly acting "a-process" of reward evoked by a stimulus must be automatically counteracted by a more slowly acting, homeostatic "b-process" that begins during presentation of the stimulus to modulate the reward but persists beyond it and provides an aversive signal, serving to further promote pursuit of the stimulus through negative reinforcement [39, 40]. In this view, the brain seeks to meet the challenge presented by drug effects by making a compensatory shift from a focus on reward to a focus on "anti-reward," which facilitates a shift over time from *impulsive* behavior driven by the immediate positive consequences of use to *compulsive* behavior driven by the lasting negative consequences of not using. In the setting of ongoing drug use, the user shifts from homeostasis (trying to return the system to normal) to allostasis (maintaining a state of deviation from normal) [41]. As with the alterations in salience detection described in the last section, the shift from positive to negative reinforcement also depends on adaptations (plasticity) in specific neural systems—this time centered on the systems devoted to stress and negative affect.

Key Systems

Stress signaling in the brain is centered in a collection of nuclei known as the extended amygdala, which includes the central nucleus of the amygdala (CeA), the bed nucleus of the stria terminalis (BNST), and the nucleus accumbens shell (located adjacent to, but separate from, the reward-related areas of the ventral striatum). The closely related lateral habenula also plays a role in stress signaling [11]. These nuclei communicate with memory areas (the basolateral amygdala and hippocampus); a midbrain nucleus called the locus ceruleus, which produces the amine

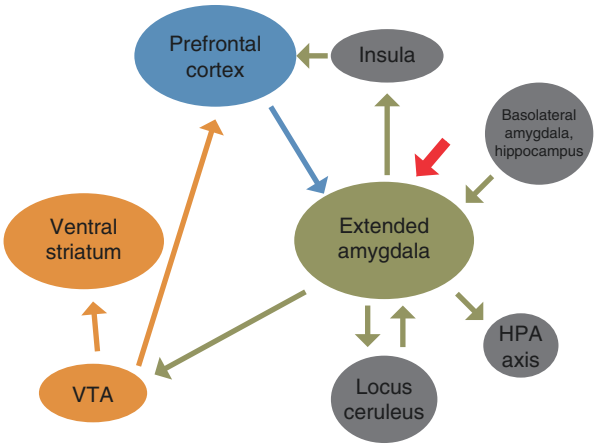

Fig. 3.4 Areas of the brain involved in stress signaling

neurotransmitter norepinephrine; and the downstream hypothalamic-pituitary-adrenal (HPA) axis governing physiologic stress responses. The extended amygdala is also in communication with the salience detection system via connections to the VTA, and with cognitive areas of the cerebral cortex via the Insula, an area of the brain governing interoception (perception of internal emotional states). Figure 3.4 presents a schematic of the extended amygdala and some of its connections to other areas.

Neurobiological Changes

In parallel with the overtraining of the salience detection system in favor of addictive substances over natural stimuli, chronic drug use causes two additional adaptations which together shift the center of gravity away from the salience system based in the ventral striatum to the stress system based in the extended amygdala [42]. First, after a period of drug exposure and exaggerated dopamine signaling, baseline reward system function is decreased. Studies in animals and humans have shown a decreased behavioral response to dopamine challenge in addicted subjects, which may be related to downregulation of dopamine receptors (specifically, D2 dopamine receptors) in the ventral striatum, as well as decreased firing of VTA neurons and dopamine transmission from the VTA to the ventral striatum and prefrontal cortex, with increased dopamine response thresholds with drug administration. This downregulation of dopamine from the VTA occurs via negative feedback mediated by neurons expressing the endogenous opioid dynorphin and projecting from the ventral striatum back to the VTA [30]. The decrease in D2 receptors in the ventral striatum also correlates with decreased activity in cognitive control areas of the prefrontal cortex, possibly through indirect inhibition of this area via a change in MSN signaling [11].

Second, persistent drug exposure followed by withdrawal evokes increased stress system function—a phenomenon seen with multiple addictive substances. In the

extended amygdala, expression of corticotropin releasing factor (CRF) is increased, leading to downstream activation of the HPA axis and increased cortisol levels at baseline and in response to stressors which, in turn, leads to an exaggerated physiologic stress response throughout the body. CRF also stimulates the locus ceruleus, causing an increase in norepinephrine signaling that adds a "fight or flight" adrenergic component to the systemic stress response and also potentiates a feed-forward loop in which norepinephrine further enhances CRF release [43]. CRF from the extended amygdala also potentiates burst (but not baseline) dopamine signaling from the VTA by activating a specific subset of dopaminergic VTA neurons that are CRF (and stress) responsive; severe/chronic stress suppresses baseline dopamine production from the VTA while burst function is maintained [44]. CRF has direct effects on the prefrontal cortex as well. It decreases the dendritic arborization (and hence the number of inputs) of pyramidal cortical cells and suppresses the pathway from the prefrontal cortex back to the extended amygdala—a potential reduction in top-down control that is also promoted by exaggerated dopamine signaling and by norepinephrine signaling [45]. All of these central changes within stress pathways are potentiated by systemic corticosteroids from the HPA axis. And other stress signals are recruited during drug abstinence in drug-dependent individuals, as well: the endogenous opioid dynorphin (expressed in the extended amygdala as well as in a negative feedback loop within the mesocorticolimbic dopamine pathway), as well as the signaling peptides vasopressin, substance P, and hypocretin (orexin), which is also involved in appetitive signaling. Anti-stress "buffer" systems come into play—including signaling by the antistress molecules neuropeptide Y, endocannabinoids, and nociception (orphanin FQ)—but are unable to neutralize the strong stress signals evoked by drug exposure and withdrawal [40, 46]. Like the changes in salience detection described earlier in this chapter, a number of these changes in stress signaling may be mediated by exaggerated dopamine signaling from the midbrain in the presence of addictive drugs, evoking cAMP signaling and downstream activation of the transcriptional regulator CREB in the ventral striatum, prefrontal cortex, and amygdala; stress related targets of CREB include the CRF and prodynorphin genes [47].

An interesting additional component of the stress response involves immune signaling within the brain, mediated by the unique cell population of microglia, which may invoke an inflammatory response in the brain under stressful conditions such as withdrawal from an addictive substance. Activation of microglia has been shown to occur after intermittent alcohol administration in young rodents, and there is evidence of inflammation in the postmortem brains of human subjects with a heavy drinking history. Microglial cell-related inflammation can occur throughout the brain and may contribute to changes in gene expression reducing frontal cortex function and sensitizing the brain's stress circuits including the extended amygdala [48].

Behavioral Effects

In animal models—in which investigators have generally used self-administration protocols to enhance the relevance to addiction in humans—a large body of

evidence now points to a mutually reinforcing relationship between stress and long-term drug use. Stress (modeled in animals in various ways, including physical restriction, foot shock, and social stress) enhances the behavioral response to addictive substances and increases drug self-administration. In addition, the application of stress during periods of abstinence promotes reinstatement of drug use (e.g., with application of foot shock in heroin-dependent rodents). The reverse is also true and has been seen in morphine-dependent rats: exposure to drugs enhances behavioral responses to stressful stimuli, such as freezing behavior or anorexia, in part due to increased basal corticosteroid levels. Withdrawal from drugs after a period of dependence causes signs of stress and negative affect even in the absence of stressful stimuli, and also makes it harder to invoke reward responses with stimulation of the salience pathway—a phenomenon of "reward resistance" induced by a wide range of addictive drugs including cocaine, amphetamines, opioids, cannabinoids, nicotine, and ethanol [49]. There is also evidence that early childhood stress in rodents (decreased maternal care or deprivation) causes increased reactivity to novelty, increased sensitivity to and self-administration of addictive substances, decreased social behavior, increased aggression, and increased fear behaviors in adulthood [50].

In these same animal models, many of these stress-related phenomena can be prevented by selective manipulation of specific stress system components. For many addictive substances, persistent drug self-administration, stress-induced reinstatement of drug use after a period of abstinence, and withdrawal-induced anxiety behaviors can all be blocked by CRF receptor blockers [40, 51]. Intracerebral administration of neuropeptide Y blocks withdrawal symptoms and increased drug intake in drug-dependent rodents [51]. And naltrexone and minocycline—both of which suppress the inflammatory function of microglial cells—can ameliorate alterations in executive function, craving, and sensitivity to alcohol ingestion seen in adult rodents who were exposed to alcohol as adolescents [48].

Human studies also point to a strong "dark side" of SUD in which negative reinforcement driven by stress and negative affect becomes a primary driving force for ongoing drug use to stave off the unpleasant physical and emotional state associated with absence of the drug. Withdrawal after multiple cycles of addictive drug use gives rise to a subjectively dysphoric state, with features including irritability, emotional pain, malaise, dysphoria, alexithymia (decreased emotional awareness), and decreased motivation for natural rewards. Even after a single infusion of cocaine, the immediate and rapidly decaying "high" is followed by a slower-onset state of negative affect that persists much longer after the infusion [36]. Human subjects with substance use disorder also develop symptoms resembling those of post-traumatic stress disorder (PTSD) including mutually reinforcing stress-related and drug-related impairments of cognition and behavioral control, as well as heightened physiologic stress responses [45]. The HPA axis is dysregulated and hyperactive—a phenomenon seen prominently in people with opioid addiction and remediated by methadone maintenance treatment. Mothers affected by SUD experience not only a reduced sense of the salience of child-related stimuli but also experience increased parenting-related stress [52]. Early childhood trauma (including emotional trauma

and neglect) causes increased novelty seeking, attachment disturbances, increased isolation, elevated markers of HPA activation (such as chronically high cortisol levels) and increased rates of comorbid depression, anxiety, and PTSD—all of which correlate with increased incidence and persistence of SUD (especially stimulant addiction) [50, 53]. Consistent with this, a recent review of human studies of stress and SUD—including childhood trauma and post-childhood stress exposures, and examining studies across multiple substances—showed that stress worsens the illness course of SUD at multiple stages including initiation, experimentation, escalation to SUD, and relapse after abstinence [53]. Taken together, these data suggest that in humans, as in experimental animals, stress can effectively set the stage for more rapid progression to severe SUD.

Changes in Cognition and Control

As part of the machinery of decision-making, both salience detection and stress responses occur automatically, operating in a bottom-up fashion under the radar of consciousness to drive behavior. But the brain also includes a top-down system for cognition and control, whose effective operation is key to managing bottom-up drives and consciously making good decisions. Some have framed this as a dialectic between an "impulsive system," driven by the amygdala and ventral striatum and encoding the immediate affective/emotional effects of stimuli, and a "reflective system" based in the cerebral cortex and encoding the more slowly generated affective/emotional correlates of longer-term outcomes [2, 7]. The reflective system involves the use of memory and imagination and recruits areas involved in sensory perception, interoception, planning, and behavioral inhibition. As a SUD becomes firmly established and changes occur in salience detection and stress signaling that bias behavior toward substance use, changes also occur in the reflective system that weaken its ability to help the individual decide, on an ongoing basis, to reshape behavior away from using the substance.

Key Systems

Figure 3.5 shows the key connections involved in the cognition and control system, focusing on the prefrontal cortex (PFC), which contains a number of specialized subregions including the dorsolateral PFC (involved in working memory and task persistence), the ventromedial PFC (involved in impulse control), the orbitofrontal cortex (involved in planning), and the anterior cingulate cortex (involved in assigning emotional valence to planned actions) [11]. In general, the dorsal areas of the PFC govern "cold" cognitive functions (such as analysis and planning, sometimes termed "System 2,") while more ventral areas govern "hot" functions (such as suppression of impulses and drives, sometimes termed "System 1".) [8, 54]. The PFC has reciprocal connections with the salience system, projecting directly to the ventral striatum and VTA and receiving modulatory input from VTA dopamine

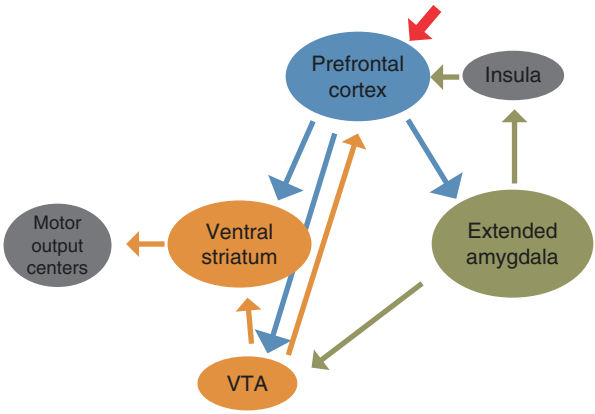

Fig. 3.5 Areas of the brain involved in cognition, control, and "reflective" processing

neurons. It also interacts with the stress system, receiving input from the extended amygdala (including modulation by CRF) as well as an encoded representation of the internal emotional state via the insula.

Neurobiological Changes

Just as the exaggerated dopamine signal triggered by addictive substances shapes the salience and stress systems to more effectively drive behavior toward drug use, it also weakens the ability of the PFC to control those systems. Activity of the PFC is inhibited by chronic exposure of the ventral striatum to dopamine, leading to over-activation of a particular population of MSNs carrying D2 dopamine receptors, which then leads (through an indirect neural pathway) to suppression of PFC activity in key areas [11]. Another site where change occurs is at the excitatory glutamatergic projection from the PFC to cells (including MSNs) in the ventral striatum, which is modulated by dopamine. A hypothesis for how this occurs has been termed the "glutamate homeostasis hypothesis," which posits that altered glutamate handling inside and outside striatal synapses impairs the regulation of striatal circuitry by the PFC and other areas [3]. In this hypothesis, a key factor is the regulation of extracellular glutamate levels in synaptic and peri-synaptic areas by glial cells, mediated by glutamate transport across the glial cell membrane via a glutamate transporter and a glutamate-cysteine co-transporter. A specific type of glutamate receptor (the metabotropic glutamate receptor) located outside the synaptic cleft is felt to play a special role in modulating synaptic transmission and plasticity caused by the pattern of glutamatergic input. In chronic drug exposure leading to hyperactive dopaminergic input to the striatum, there is a shift toward synaptic and away from extra-synaptic glutamate signaling, in part due to decreased glutamate/cysteine exchange by glial cells. In turn, this leads to a loss of synaptic plasticity (long-term potentiation and long-term depression), causing a possible loss of information from some synaptic stimulation patterns. There are also dopamine-related structural changes at these specific top-down synapses, including an increased number of dendritic spines, a widening of

individual spines, and possible formation/recruitment of new "silent synapses" with specific higher-conductance glutamate receptor subunits, whose presence correlates with increased liability to cue-related relapse [3, 11, 55].

Other data suggest structural changes within the reflective system nuclei, such as reduced gray matter density in PFC subregions and decreased dendritic spine density in orbitofrontal cortex cells in stimulant-dependent rodents, as well as impaired remodeling of this region during training on other tasks [56]. Imaging studies in human subjects also show changes in the function of the PFC, such as decreased baseline metabolic activity of the orbitofrontal cortex and PFC correlated with reduced dopamine receptor density in the ventral striatum—a consistent finding with numerous addictive substances including cocaine, methamphetamine, nicotine and alcohol. During challenges with drugs or drug cues, increased activation of the orbitofrontal cortex and PFC occurs and is proportional to the intensity of subjective craving. Other drug-related changes in the PFC appear to be drug-specific, such as a long-lasting decrease in endogenous opioid receptors in the PFC in people who use cocaine and a decrease in serotonin receptors in the PFC in people who use methamphetamine [8, 57]. There may be a shift away from a reliance on "cold/system 2" processing toward "hot/system 1" processing as a SUD becomes established [10, 57].

Optogenetic studies in animals, in which the electrical activity of specific cell populations can be selectively manipulated—show a reproducible correlation between PFC cell function (specifically, the function of the principal glutamatergic pyramidal cells) and control of behavior in self-administration models. Rodents who self-administer cocaine have decreased PFC pyramidal cell excitability at baseline, and restoration or further disruption of excitability through optogenetic manipulation can strengthen or weaken behavioral control, respectively. Other experiments have shown that the pattern of striatal stimulation by PFC inputs matters; repetitive stimulation of striatal MSNs via specific projections from the PFC can cause a long-lasting reversal of recruitment of silent synapses and cue-induced cocaine seeking that may represent "unlearning" of previously established neurobiological adaptations [6].

Developmental and genetic studies in humans also point to a link between exposure to addictive substances, specific susceptibility genes, and PFC function. For example, people with certain cannabinoid receptor alleles who use cannabis have increased cue reactivity in the PFC; carriers of a monoamine oxidase A genotype with low activity of the enzyme have decreased gray matter density in the orbitofrontal cortex and a higher rate of lifetime cocaine use; and children of parents with alcohol use disorder have a hypoactive orbitofrontal cortex correlating with a higher susceptibility to alcohol use disorder in later life. With all of these correlations, it remains unclear whether PFC dysfunction and its consequences precedes drug use (i.e., is a predisposing factor) or is a consequence of drug use, or whether both could be true [11, 47, 58, 59].

Behavioral Effects

Dysfunction in the PFC and its subregions in patients with SUD have been associated with a cluster of executive function deficits termed the "IRISA syndrome"

(named for a pattern of Impaired Response Inhibition and Salience Attribution). In this syndrome, drugs and drug-related cues take on an increased salience that is accompanied by deficits in domains including self-control, emotional regulation, drive/persistence, self-awareness, flexible attention/task shifting, working memory, learning/long-term memory, and planning/valuation of options [8]. Some have described the results of PFC dysfunction as a "myopia for future consequences" that resembles those seen in patients with traumatic or stroke-related PFC damage—intelligence and long-term memory function normally but there are dramatic effects seen on emotion, social behavior, and decision-making as objectively measured by tests such as the Iowa Gambling Task. Interestingly, there is a wide variability of performance on this task, with only 67% of SUD patients performing like patients with PFC damage and the other 37% performing like normal subjects [7, 56]. Others have sorted the decision-making deficits seen in severe SUD into two clinically distinct scenarios that may require different approaches to treatment: impulsive decision-making (e.g., delay discounting) and drug versus nondrug decision-making [60].

As mentioned at the start of this section, particular subregions of the PFC govern specific cognitive processes that may have particular clinical significance. One subregion of the PFC, the orbitofrontal cortex (OFC), which has reciprocal connections to the amygdala, ventral striatum and sensory cortex, may play a special role in the expectation of outcome and the correction of behavior to shape that outcome. Similar to patients with brain damage affecting the OFC, patients with severe SUD may have difficulty generating a predictive, comparative signal that can be used to modify future behavior [56, 61]. Response inhibition is another specific behavioral function governed primarily by the ventrolateral portion of the prefrontal cortex that also has a special importance in addiction. Impairments in this function—measurable in specific cognitive tasks and similar to deficits seen in psychiatric disorders such as ADHD and OCD—are well documented in stimulant addiction and may also be linked with alcohol and nicotine use. These impairments often co-occur with complementary deficits such as rigidity and perseveration that reside in other areas of the PFC (such as the ventromedial PFC and OFC). In human subjects, these and other patterns of cognitive dysfunction seen in the context of severe SUD are linked with negative outcomes such as increased drug use, decreased performance on neuropsychiatric testing, and increased vulnerability to relapse [62].

In addition, neuroimaging findings—often combined with cognitive testing—confirm the association between PFC dysfunction and specific cognitive deficits. PET imaging abnormalities in patients addicted to cocaine correlate with poor performance on gambling tasks, and fMRI imaging studies in a similar population show an increase in PFC response to drug-related words that is associated with a strong attention bias toward those words. While most of the initial neuroimaging and cognitive testing data has been collected in patients with cocaine use disorder, impaired PFC-dependent decision-making has now been seen with multiple addictive substances including alcohol, cannabis, cocaine, opioids, and methamphetamine, a substance which may have the most profound effects on cognition [8, 11, 37].

Neurobiology of Opioid Addiction

Perhaps more convincingly than other substance use disorders, opioid addiction gives credence to the still somewhat controversial idea that both positive and negative reinforcement are important in the genesis of addiction [35]. On the one hand, opioids have powerful analgesic and anxiolytic properties that can be powerfully reinforcing. On the other hand, withdrawal from opioids has strongly aversive features, both affective and physiological, many mediated by stress-related neurotransmitters such as norepinephrine and CRF. In this sense, opioid addiction may differ from psychostimulant addiction in that the "dark side" of aversive states and the process of learning from them may have a special significance [63]. In fact, one could consider opioid addiction as a model disorder with which to highlight the neuroadaptations occurring in all three brain systems recruited during the genesis of severe SUD: salience detection, stress processing, and cognition/control. Neuroadaptations on different time scales and at different neurobiological levels (molecular, cellular, and circuit) lead to short-term withdrawal effects, negative affective states associated with protracted abstinence, and long-lasting learning and memory leading to a long-term susceptibility to relapse.

Opioid-Related Neuroadaptations

At the molecular and cellular levels, the site of action of opioids is at the mu opioid receptor—a G-protein coupled transmembrane receptor that couples to inhibitory ion channels in the neuronal membrane and also inhibits the cAMP intracellular signaling pathway. This has the effect of suppressing the electrical excitability of neurons containing mu opioid receptors, and also inhibits modification of CREB, with downstream effects on gene expression [64, 65]. Homeostatic molecular and cellular adjustments in the presence of opioid agonists work against these direct effects of opioids to maintain the cellular status quo in the face of excess opioid-mediated signaling. For example, with consistent receptor activation, there is downregulation of opioid receptors (via internalization from the neuronal membrane) causing receptor tolerance—an effect that is stronger for methadone and other synthetic opioids than for morphine [65]. In addition, in response to suppression of the cAMP pathway via mu opioid receptors, there is a compensatory increase in cAMP signaling that adjusts electrical excitability upward and increases synthesis of norepinephrine. All of these adaptations serve to return the function of cells to normal in the presence of excess exogenous opioids, but result in cellular hyperexcitability when opioids are removed. A particularly prominent example of this phenomenon occurs in the locus ceruleus, whose cells are the primary source of norepinephrine in the brain and are heavily invested with opioid receptors. Excitability of this area is markedly suppressed by opioids, but with long-term opioid exposure, compensatory changes occur that eventually restore normal function. Therefore, the nucleus becomes markedly hyperactive, with excessive production of norepinephrine in the opioid withdrawal state [64], leading to

enhanced stress signaling in the brain and a markedly enhanced "fight or flight" physiological response.

At the neural circuit level, there are changes in pathways directly affected by opioids (such as the projections from the locus ceruleus) as well as "pass-forward" changes affecting neurons not directly affected by opioids. In the VTA, opioids cause a de-repression of dopaminergic neurons that enhances dopamine transmission to the ventral striatum and prefrontal cortex. In addition, through direct neuronal effects and indirect effects (such as changes in dopamine signaling), long-term synaptic changes (via processes such as LTD and LTP) and structural neuronal changes occur in brain regions such as the VTA and hippocampus in response to opioids. According to their receptor specificity, exogenous opioids also often directly affect endogenous opioid pathways, such as the dynorphin-mediated negative feedback pathway from the ventral striatum to the VTA and Nociceptin/ORL-1 input to the VTA from the hypothalamus, thereby modifying key modulatory mechanisms in the brain more directly than other addictive substances. Opioids are also able to activate microglial cells, leading to inflammatory cytokine and neurotrophic factor release and further affecting synaptic plasticity and, with withdrawal of opioids, the genesis of aversive short- and long-term withdrawal states [48, 63, 64].

Opioid Effects on Salience Detection

Unlike stimulants, which directly act to enhance salience signaling via dopamine in the ventral striatum, the primary action of opioids on the salience detection pathway is upstream from the ventral striatum, in the VTA. As noted earlier in the chapter, the dopaminergic pathway from VTA to ventral striatum, prefrontal cortex, and other brain areas (such as the hippocampus) may encode a "reward prediction error" signal, giving rise to positive reinforcement—with long-lasting associative memory—in the setting of novel rewarding stimuli [23]. Within the VTA, there are dopaminergic neurons of several types (including a sub population that may signal the salience of aversive stimuli specifically), as well as GABA-ergic and glutamatergic neurons that project to many of the same targets [66]. The VTA is the primary site of opioids' action on the mesolimbic dopaminergic pathway, as a large proportion of axon terminals (belonging to neurons projecting from elsewhere) and cell bodies/dendrites of VTA neurons express opioid receptors. Mu opioid receptors in the VTA have been shown to be essential for opioid reward and its behavioral correlates in animal models, such as conditioned place preference. As above, opioid action at mu opioid receptors inhibits local GABA-ergic interneurons, which disinhibits VTA dopamine neurons projecting to the nucleus accumbens. Mu receptor activation also inhibits GABA-ergic synapses projecting from elsewhere (e.g., the rostral medial tegmental nucleus, an important modulator of the VTA) and inhibits glutamate release from other terminals synapsing onto VTA neurons (e.g., from the prefrontal cortex) [23]. Interestingly, other experiments in animal models—including electrophysiological recordings in brain slices-- have suggested that opioids may directly excite a small population of VTA dopamine neurons via an opioid-sensitive calcium

ion channel, and may indirectly affect cells in the VTA via opioid-induced decreases in local extracellular dopamine concentrations [66]. There are likely also dopamine-independent pathways for the reinforcing effects of opioids, since in opioid-naïve rats, the reinforcing effects of opioids persist even with full blockade of dopamine signaling [23].

Opioids can cause long-term structural and functional changes in the salience detection pathway. It has been shown that morphine blocks long-term potentiation of GABA-ergic transmission onto dopaminergic VTA neurons, leading to a long-lasting reduction in inhibitory control over VTA dopamine neuron firing. In the ventral striatum, chronic morphine administration and then withdrawal gives rise to long-term synaptic change via a redistribution of glutamate receptors and a reduction in glutamate receptor-dependent long-term depression [65]. Furthermore, in the hippocampus, chronic opioid administration leads to decreased long-term potentiation in hippocampal cells during withdrawal, giving rise to deficits in spatial learning and correlating with setting-specific morphine-related learning; this adaptation depends on long-term upregulation of cAMP pathways [65]. In some cases, there are structural changes in neurons linked to mu opioid receptor-related intracellular signaling and changes in gene expression—e.g., a reduction in size of VTA dopamine neurons after chronic opioid exposure, associated with increased neuron firing frequency. These structural and functional changes differ from those seen in the medium spiny neurons of the ventral striatum in response to dopamine (i.e., an increase in dendritic spines and dendritic branching) [23, 63]. Another longer-term effect of morphine exposure on the salience detection system may be a switch from activation of the ventral striatum by drug stimuli and cues to activation of the dorsal striatum, which may play a role in the aforementioned transition from the pursuit of novel stimuli to habitual/compulsive behavior; Mu opioid receptor activation in the VTA enhances the strength of dopaminergic input to the dorsal striatum, which enhances long-lasting gene expression changes there via isoforms of the FOS regulatory protein [23].

Interestingly, acute and chronic pain can also affect the salience detection system, with implications for opioid addiction. Acute pain causes dopamine release from specific VTA dopaminergic neurons (possibly the proposed special population tuned to aversive, rather than rewarding, stimuli), potentially attributing a salience signal to the aversive stimulus. Chronic pain causes a chronic hypo-dopaminergic state throughout the mesocorticolimbic dopaminergic system with decreased reward responsiveness, anhedonia, and decreased effects of opioids on the salience pathway (although they may still retain their analgesic effect, which affects clinical behavior). This is a "dark side"-like state that resembles the antireward phase of late addiction, although it is not clear if a long-term state of chronic pain causes an increased susceptibility to substance use disorder in all patients [66].

Opioid Effects on Stress Systems

Negative reinforcement plays a particularly important role in driving opioid addiction, via prominent withdrawal symptoms and related negative affect including fear

of withdrawal. This leads to a long-lasting learned association between the administration of opioids and relief from an aversive state; notably, shorter-acting opioids such as heroin and fentanyl are particularly powerful promoters of this learning mechanism since they allow more trials over which to learn the association [63]. This process—in which there is deep learning related to the "trauma" of opioid withdrawal—may explain why there is significant comorbidity between opioid use disorder, PTSD, depression, and other stress states [67, 68]. Stress-related relapse is a prominent feature of opioid use disorder and is seen in both animal models and human subjects. Particularly interesting is evidence from ecological momentary assessment (EMA) studies, in which participants on buprenorphine or methadone-maintenance treatment of opioid use disorder use electronic diaries to self-report their experiences of stress and craving as they go about their normal activities. EMA studies have shown a strong and independent relationship between stress and craving, and suggest that stress may also potentiate the well-established relationship between drug cues and craving, thus dually increasing vulnerability to relapse [69]. Fear of withdrawal is also a major reason patients continue methadone or buprenorphine maintenance treatment [63], and larger-scale environmental stressors are theorized to have had a profound impact on opioid addiction epidemiology: examples include the Vietnam war [70] and contemporary socioeconomic trends in rural and formerly industrial areas of the U.S [71].

As above, the direct suppressive effects of opioids on the electrical excitability of neurons of the locus ceruleus cause cellular adaptations that restore excitability to normal in the presence of opioids but lead to high noradrenergic tone when opioids are withdrawn. The locus ceruleus also becomes less sensitive to stress-related CRF input from the amygdala in the presence of chronic opioids, leading to a hypersensitivity to CRF (and therefore stress) during withdrawal and protracted abstinence [72]. Norepinephrine from the locus ceruleus has downstream physiological effects, but also central effects on the extended amygdala, which then projects to the VTA via input pathways that are modulated by morphine.

Other components of the stress signaling pathways of the brain are modulated by opioids. The basolateral amygdala is involved in the retrieval of opioid cue memories, as proven by lesioning experiments in rodents. The projection of this area to the prefrontal cortex has been proven to be important in consolidating morphine-related memories, and is dependent on the VTA-PFC dopaminergic projection that is modulated by morphine; output of the basolateral amygdala to the central nucleus of the amygdala is also directly affected by morphine. The paraventricular nucleus of the thalamus (PVT), which plays a role in aversive learning, is felt to play a key role in conveying memories of the aversive state of opioid withdrawal to the extended amygdala and cortex as well as the ventral striatum. Mu opioid receptors in the lateral hypothalamus affect orexin input to the VTA through long-term changes in gene expression via cAMP, CREB, and FOS pathways; in the VTA, orexin acts at orexin-1 receptors on dopamine neurons that are also modulated locally by opioids. A neuroimmune response via microglial cells within the limbic system—including release of biologically active chemicals like cytokines, chemokines, and growth

factors that can cause structural changes in neurons (such as changes in spine density and axonal targeting)—may be promoted by chronic opioids via direct binding of opioids to an accessory protein of the Toll-like receptor-4 molecule. Interestingly, opioid-inactive variants of the opioid antagonists naloxone and naltrexone can block this signaling as well as the affective symptoms and other signs of long-term opioid withdrawal [63, 65]. Finally, the antistress endocannabinoid system has significant cross talk with the opioid system within stress circuits. For example, in the locus ceruleus, mu opioid receptor/cannabinoid receptor complexes may form, affecting G-protein coupling and intracellular cAMP signaling [72].

Opioid Effects on Cognition and Control Systems

While most studies of changes in top-down control pathways in the genesis of substance use disorder have been done using stimulants, it is now clear that opioid use disorder similarly involves effects on the impulse control functions such as response inhibition, centered in the prefrontal cortex (PFC) and its various subregions. After a period of chronic opioid exposure (e.g., heroin self-administration in rodents), excitatory glutamatergic input to PFC cells is decreased. Similarly, during periods of abstinence, opioid cues trigger increased inhibitory GABA-ergic input to these cells. Both changes reduce PFC activity and output to other brain regions, which correlates with impaired regulation of opioid seeking behavior in animal models. In addition, via its effects within the VTA described above, morphine enhances dopaminergic signaling in the ventral striatum and the PFC, thereby evoking the same types of adaptations in ventral striatal and PFC function that occur in stimulant addiction, and similarly reduce the effectiveness of both "hot" (System 1) and "cold" (System 2) cognitive control over decision-making. Interestingly, for opioids but not for other addictive substances, dopamine signaling in the PFC has been shown to be modulated by endocannabinoids; increased endocannabinoid transmission blunts and decreased transmission enhances motivated behavior toward morphine, possibly via modulation of the glutamatergic connections from the PFC back to the VTA [23].

In human subjects with opioid use disorder, structural changes in cognitive control areas (including the PFC) have been noted. A meta-analysis of 12 high-quality neuroimaging studies in patients with opioid use disorder—primarily men with heroin addiction—showed reductions in gray matter in the frontotemporal regions bilaterally (including orbitofrontal cortex) and decreases in gray matter in the left cerebellar vermis and right insula that were dependent on length of opioid use. These structural deficits largely recovered with increasing length of abstinence, and some recovery of frontal cortex gray matter was seen with methadone maintenance. There was no difference in these effects between people who used heroin and those who used other opioids. The results suggested structural "damage" to two circuits: (a) a frontal-cerebellar circuit that could mediate problems with impulsivity, compulsive behavior, and affective states and (b) a frontal-insular circuit that could mediate problems with cognition and decision-making [73].

Conclusion: Toward a Framework for Recovery

While addiction (severe SUD) is certainly a multifactorial disorder of decision-making, this chapter makes the argument that addiction, like other conditions in which neurobiological changes play an essential role in the development and natural history of symptoms, is—at least in part—a chronic brain disorder. The neurobiological changes that occur in the genesis of addiction involve two "bottom-up" systems (one for salience detection and one for stress signaling) and a "top-down" system for cognition and control of behavior, and adaptation in all three systems in the presence of an addictive drug occurs simultaneously. On a shorter time scale, these adaptations encode the attachment of exaggerated importance/salience to drug stimuli which fuels the initial phases of addiction. On a longer time scale, adaptations in these neural pathways lead to (a) the emergence of opposing aversive states that kick in when the drug is removed and (b) a reduced ability to keep in check drug-seeking behaviors that are driven by the enhanced salience of the drug and the desire to avoid the aversive abstinence state. All of these short- and long-term adaptations can become hardened by structural and functional re-wiring of neural pathways, which—via associative (Pavlovian) and instrumental (Skinnerian) learning mechanisms—results in a learned inability to control drug use behaviors [74]. And it is precisely this loss of control, neurobiologically learned during the genesis of SUD, which underlies one of the clinical hallmarks of addiction—a vulnerability to relapse that persists long into a period of abstinence.

Nevertheless—to quote Satel and Lilienfeld [9], "neurobiology is not destiny," and people affected by severe SUD have a tremendous capacity to achieve and sustain remission and recovery. Studies in animal models show that while the behavioral effects of drug exposure (particularly psychostimulant exposure) can be very long-lasting—and some may even be potentiated by length of abstinence (see, for example, the "incubation" of cue responses described in previous sections) [26]—many of the neurobiological changes discussed here are reversible with time. In human subjects, multiple types of neuroimaging studies, including PET studies [11, 37, 54] and even more anatomically precise scanning modalities such as MRI or CT [73], show evidence that specific types of neurobiological "damage" wrought by addictive substances can be reversible with time in recovery, including recovery supported by medication for addiction treatment. While skepticism is warranted about applying a purely medical model to addiction and recovery, understanding the neurobiology of addiction can help organize our thinking about the clinical features and "biomarkers" of the disorder [75]. Perhaps most importantly, understanding addiction neurobiology holds promise for allowing innovation of new pharmacologic and nonpharmacologic treatments—or new combinations of treatments—that may serve as additional pathways toward recovery from severe SUD.

Figure 3.6a, b shows how a framework for addiction as a disorder of choice can become a framework for thinking about treatments to promote recovery. Figure 3.6a shows how external factors affecting decision-making in SUD—including effects of substance use itself—can be addressed by various components of treatment including social support, therapeutic communities, mutual support groups, prevention

strategies, and strategies for reduction in negative consequences (harm reduction). In addition, we highlight the importance of regular primary care and psychiatric care for patients recovering from substance use disorder—components that have great power to proactively recognize and treat the medical and psychosocial effects of SUD but which are often under-utilized due to stigma, treatment system disconnection, and a lack of team-based and community-based care.

Figure 3.6b includes the issue of addressing physiological withdrawal with medically supervised withdrawal or pharmacologic maintenance therapy (currently most often used in the case of opioids), and also shows how the three components of the neurobiological pathogenesis of addiction (salience detection, stress signaling, and cognitive behavioral control) may be individually and collectively addressed by specific types of therapies. Some treatments (such as maintenance therapy, in the case of opioid addiction, drug-metabolizing enzymes, or immunologic approaches such as drug vaccines) could stabilize all three pathways [76], while other treatment modalities address particular components of the neurobiological machinery.

For example, for the changes in salience detection that occur in addiction, novel nonpharmacologic and pharmacologic therapies could include [12, 74]:

- Contingency management, to help reassign salience to less harmful stimuli.
- Dopamine D3 receptor antagonists, which may block some of the dopamine-induced changes in the ventral striatum and corticostriatal pathways without the motor side effects of other dopaminergic blockers and may be particularly effective in methamphetamine addiction.
- Novel mu opioid receptor antagonists.

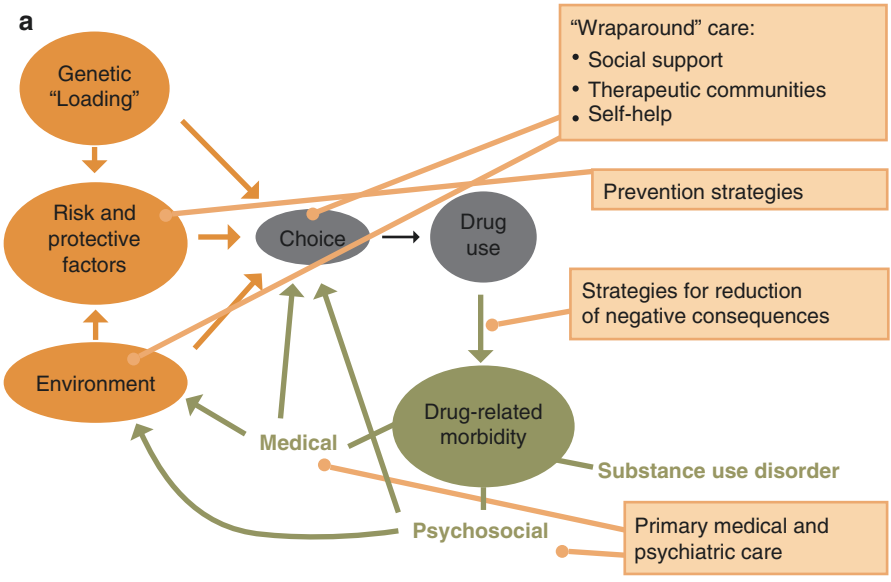

Fig. 3.6 From a framework for addiction toward a framework for recovery

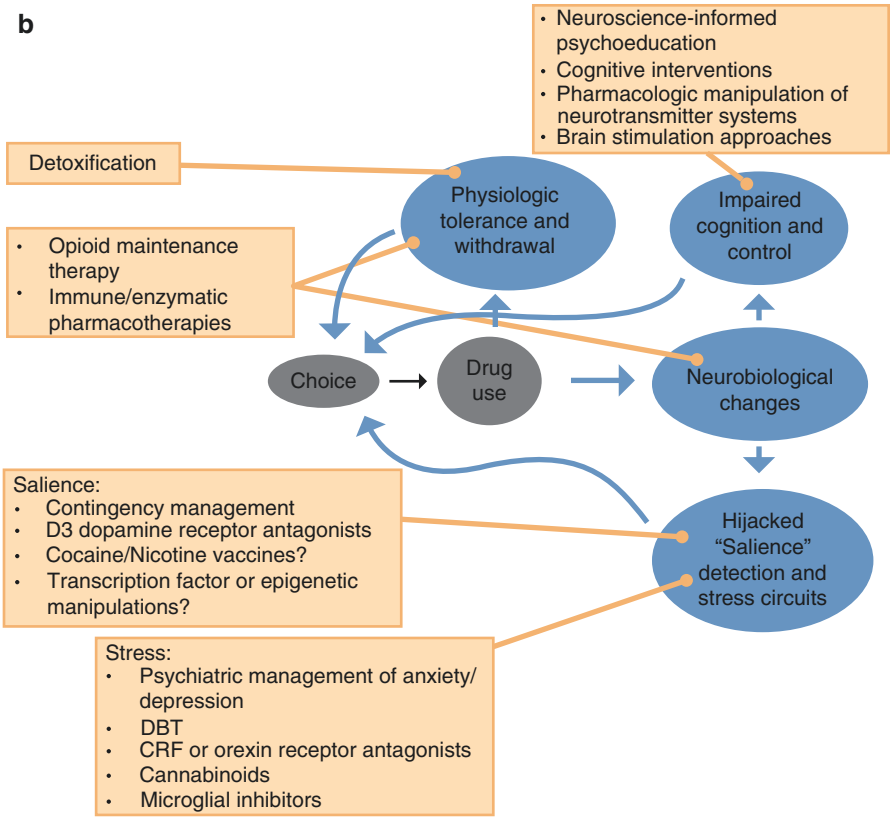

Fig. 3.6 (continued)

- Selective GABA agonists to suppress drug-related VTA dopamine release.
- Drugs that act on intracellular messenger pathways, such as selective phosphodiesterase inhibitors which affect cAMP signaling.
- Specific types of glutamate receptor agonists or N-acetylcysteine to normalize glutamate homeostasis in the ventral striatum (the latter approach well tolerated in humans and already shown to reduce cocaine, nicotine, and cannabis use in human studies and cocaine seeking in animal models).

For adaptations in stress pathways, novel therapies could include [12, 76–78]:

- Effective psychiatric management of stress states, including pharmacologic treatment of anxiety or depression and modalities such as dialectical behavioral therapy for trauma symptoms.
- Alpha-2 adrenergic agonists (such as clonidine and lofexidine) or adrenergic blockers (such as propranolol or carvedilol) to inhibit the production or effects of norepinephrine from the locus ceruleus.
- CRF or orexin receptor antagonists.

- Cannabinoid receptor agonists, to enhance the neurobiological anti-stress "buffer system."
- Microglial inhibitors (such as minocycline or naloxone/naltrexone analogs), to reduce neuroinflammation.

And for changes in prefrontal cortex-based cognition and control functions, novel approaches could include:

- Therapeutic modalities such as neurobiologically informed psychoeducation [79].
- Cognitive interventions (such as cognitive-behavioral therapy, cognitive inhibition, motivational enhancement therapy, affect regulation, mindfulness training, episodic future thinking, or fMRI/EEG neurofeedback), many of which have been shown to improve behavioral control and normalize neuroimaging findings in SUD [75, 80, 81].
- Pharmacologic approaches (such as D-cycloserine, modafinil, atomoxetine, memantine, galantamine, bupropion, methylphenidate, buspirone or citalopram) that affect the activity of specific neurotransmitters including norepinephrine, acetylcholine, glutamate, dopamine, and serotonin and may enhance the activity of areas of the PFC that govern specific functions such as response inhibition [74, 76, 82].
- Antisense "knockdown" of protein expression in areas such as the amygdala where conditioned memories are consolidated [74].
- Targeted "extinction" training to "erase" drug memories (a behavioral method that has been trialed in both rats and humans) [83].
- Transcranial or deep brain stimulation at physiological frequencies targeting specific areas such as the ventrolateral PFC (for response inhibition) or dorsolateral PFC (for craving) to help bolster long-term recovery [11, 16, 54].

In order to be successful, these varied lines of attack—all deeply informed by neuroscience—will need to be applied in temporally specific combinations that are tailored to individual patients' needs, with an understanding of the different routes to addiction experienced by patients and the diverse ways in which SUD is expressed, even within each class of addictive substance. And these treatments will need to be deployed as part of a comprehensive treatment strategy and bioethical view that values human agency in recovery and acknowledges addiction as in part a difficult to treat chronic brain disorder, without falling prey to the false choice that people struggling with SUD are either "sick" or "bad" [9, 10, 54].

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Terminology and Conceptualization of Opioid Use Disorder and Implications for Treatment

4

Richard Saitz

Using correct terminology has implications for clinical care, research, and public policy relevant to opioid use disorder. In order to know what treatment has efficacy, the condition being treated must be clearly defined, described, and named. In order to study a new treatment and know that it will work for others, the condition must be accurately described. In order to communicate about opioid use and related conditions with policy-makers, the condition needs to be clearly delineated. Beyond research and clinical care efficacy, the experiences of people with addiction in health-care settings and society are greatly affected by how they are viewed. Words impact how people think (including clinicians, scientists, and policy-makers), and as such, they can affect the effectiveness of care and public policy. As a result, use of accurate nonstigmatizing terminology is not only respectful, it is essential for high-quality clinical care, research, and public health practice.

The history of addiction is rich with the use of colorful terms in the lay press that evoke fear. But clinical and scientific terms have often reflected societal views. In the past, addiction was conceptualized as a moral failing. Treatments were not systematically studied like they have been for other medical illnesses. Treatments were delivered in nonclinical settings with much reliance on social interventions. Even when well-meaning, or with lack of recognition of the implications, and even when preferred by those affected, terms such as addict or inebriate affect how people are seen and how they see themselves (as a disease or condition, rather than a person with a disease or condition). The main purpose of proper terminology, however, is accuracy, and not political correctness. As a secondary effect, stigma may be minimized to favorable effect. But it is unlikely that stigma will ever be eliminated, and

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some stigma may even have beneficial effects. For example, societal level stigmatization of smoking likely had much to do with public policy that contributed to a very substantial decline in smoking. However, when stigma is so powerful that people are exclusively defined by their behavior to the extent they are not viewed as people, such potential benefits are outweighed.

Although inaccurate and stigmatizing terms continue to pervade addiction-related clinical, scientific, and public discourse, consensus is emerging around accurate and less stigmatizing terminology. This terminology has implications for people with addiction in general, opioid addiction, and for treatment. Although not exhaustive, this chapter discusses major issues in terminology and provides suggested terms to use and avoid. As the field evolves further, terminology will evolve, ideally consistent with the scientific understanding of the disease.

Conceptualization of Opioid Addiction

Opioid addiction is a health condition and for some it is chronic and recurrent. Although disease is essentially a social construct, there is widespread agreement that it involves a disturbance in structure or function. Furthermore, biological, psychological, and social factors are involved in the causes and manifestations of addiction, contributing in similar proportions as is the case for other diseases. For example, genetics explain about half of the risk for addiction.

"Opioid addiction," (or "addiction"), "opioid use disorder," and "opioid dependence" are considered roughly synonymous. They refer to a health condition or disease that involves opioid use. I will return to the complexity in the term dependence later in the chapter. "Addiction" is often used by laypersons, and it is defined by one professional society, the American Society of Addiction Medicine (ASAM) in a consensus policy statement as being "characterized by an inability to consistently abstain, impairment in behavioral control, craving, diminished recognition of significant problems with one's behaviors and interpersonal relationships, and a dysfunctional emotional response [1]." One challenge that arises in using the term addiction is that although it is very well described, there are no specified criteria, tools, or algorithms that have been validated for determining whether it is present or absent in an individual. Thus, the term has an accepted definition and can be recommended for use, but it is limited in its ability to characterize people with the condition definitively. Related to this issue of lack of criteria, studies of treatment and prognosis include people with conditions that are defined by criteria that are applied using validated tools. Thus, if one uses the term "addiction" clinically, or if one wants to know if an addiction treatment has efficacy, one must extrapolate from studies of people with conditions defined in other ways.

In contrast, two diagnostic terms are recognized internationally that have tested criteria and corresponding validated tools for assessment: "opioid use disorder" (a specific type of substance use disorder) and "opioid dependence" (dependence with the substance specified). The former is a term promulgated by the American Psychiatric Association (APA) and the latter by the World Health Organization

[2–5]. An APA committee that defined the disease of addiction agreed on the definition but disagreed on the term used to refer to it [6]. For the Diagnostic and Statistical Manual of Mental Disorders (DSM)'s fourth edition, the term "dependence" was chosen and for the fifth edition in 2013 the term "use disorder" was chosen. Both terms have thus been used in the United States to refer to the disease. The fourth edition had two terms for the disorder: "abuse" and "dependence." These were replaced in the fifth edition with one term, "use disorder" based in part on evidence that there was one syndrome that had a range of severity (in contrast to two distinct disorders) [5].

The DSM fifth edition comments on "addiction," noting that it is often used to describe "severe problems" "related to compulsive and habitual use of substances," and "more extreme presentations." The DSM does not state that "addiction" should only mean "severe" substance use disorder. Thus "addiction" could be present in someone with a milder disorder. A mild disorder may be a stage in a progression to a more severe disorder, or it may not.

A DSM-defined opioid use disorder is a problematic pattern of use that leads to impairment that is clinically important. People with the disorder meet at least 2 criteria of 11. These criteria include taking larger amounts or using opioids for a longer time than intended; uncontrolled use, persistent desire to use, or an inability to cut down; much time spent getting, using, or recovering from the effects of use; craving; being unable to fulfill employment, home, or school roles; having recurring consequences in social spheres because of use; giving up important activities due to use; using in situations in which it would be hazardous; using despite knowing one is being harmed (physical or psychological); tolerance; and withdrawal.

"Dependence syndrome" or "dependence," as a "mental and behavioral disorder due to use of opioids" is a diagnostic term used as part of the tenth edition of the International Classification of Diseases (ICD-10). Criteria for this syndrome are similar to some of those for opioid use disorder (craving, compulsion, difficulty controlling use, tolerance and withdrawal, much time spent on the substance, giving up activities, and continuing to use despite known harm). The ICD also includes "harmful use," use that has resulted in physical or mental damage [2]. Proposed changes for the eleventh edition of the ICD include a diagnostic category for a single episode of harmful use, and specification of harmful use as continuous or episodic, and inclusion of harm to others as harmful use [7].

If the term "dependence" is used, one should clearly specify whether one is referring to the ICD-defined disorder, to the older DSM disorder of dependence, or to physical dependence. Without specifying, the term is confusing because it could mean a disease or condition (ICD, DSM-IV, or earlier) or a physiological phenomenon that is expected with regular intake of a medication or substance associated with tolerance or withdrawal. People treated with opioids for pain that take opioids as directed and regularly, will develop physical dependence, which is not a disease, and is instead a normal physiological adaptation. Of note, the criteria of "tolerance" and "withdrawal" do not "count" toward making the diagnosis of opioid use disorder when they are solely met by people taking opioids under medical supervision.

Conceptualization of Opioid Use that Risks Health Consequences

In addition to opioid use disorder, addiction, and dependence (the disease), there are other opioid use exposures that warrant attention from a health professional or that risk health consequences. In the next (eleventh) ICD edition, the term hazardous will be introduced, meaning use that increases the risk for health consequences to self or others and warrants health professional attention. The term hazardous has already been in widespread use along with others to indicate risk.

The spectrum of opioid use ranges from none or low-risk use (whether illicit or not), through use that risks consequences, to use with consequences, including a disorder [8, 9]. Aside from none or low-risk use, the spectrum is known as "unhealthy use" (Fig. 4.1). Unhealthy use includes all use that risks consequences through to addiction. Unhealthy use is the main concern for health interventions and prevention. It is defined based on current scientific knowledge by clinical and public health consensus and the definition can change with the science or consensus. The term "unhealthy" does not imply that there is use that improves health, though for some, use of opioids as directed may well improve pain, function, and, therefore, health.

Low-risk use (or lower-risk use) or no use refers to consumption of opioids in amounts or in a manner unlikely to cause harm. An example is opioids taken as prescribed for pain, or used in small amounts infrequently and not in physically hazardous situations, even if illicitly. Hazardous use or at-risk or risky use refers to use that increases the risk for health consequences [10, 11]. Examples might be use prior to operating a motor vehicle, or monthly use of an illicit opioid where the composition and amount of what is taken is unknown. These terms do not refer to use that has already led to health consequences. For opioids, there are no clear milligram or dose thresholds that define hazardous use though observational studies suggest that higher morphine equivalent amounts are associated with risk for overdose and death.

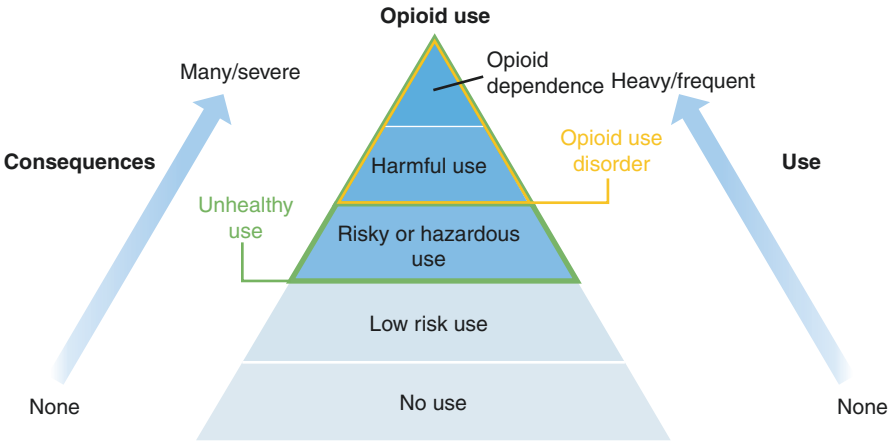

Fig. 4.1 The spectrum of opioid use and consequences

Nonmedical use, including using more than what is prescribed, can be hazardous. Use of opioids with benzodiazepines or alcohol can lead to hazardous sedative effects. Any use by youth can increase risk for later consequences. Nonmedical use by people with a family history of addiction may increase their personal risk for addiction.

Terminology for Opioid Use that Risks Health Consequences

"Misuse" can be a confusing term, though it may well have a role in describing opioid use. The World Health Organization defines misuse as use not consistent with legal or medical guidelines [3]. Because some opioids are prescribed medications, they can be used as directed or prescribed or as proven effective for treating medical conditions or they can be used otherwise—more than prescribed or without a prescription, known as misuse. "Misuse" is also used to describe not taking other medications as directed or missing doses (e.g., of a diabetes medicine). "Misuse" has also been used to describe the entire spectrum from risky use through disorder, often as a descriptor for someone who has screened positive for unhealthy use. But severe "misuse" is not a useful description of addiction, because it implies an error or an accident or a choice rather than a disorder. "Nonmedical" can be an alternative to the term "misuse" for opioids, but it isn't always adequate as a term because medically prescribed opioids can also be misused. Thus, the term "misuse" can be useful but should always be clearly defined when employed. It describes a phenomenon but not its severity; misuse is unhealthy use but it can be hazardous or a disorder. "Problem" use is a term that is not particularly useful. It is often used to describe a condition that has not been well defined. Problem use can refer to harmful use (use with a consequence) or to the spectrum of unhealthy use, and conversations with patients about "problem use" is often unproductive. "Inappropriate" is yet another term that carries judgment, is defined variously, and is not useful. "Abuse" should be avoided even in the term "abuse potential" or "abuse liability" which is commonly used in studies of medications or drugs that aim to determine addiction risk. "Addiction liability" and "addictive potential" are better.

Terminology for opioid use should therefore include no use, use, low- or lower-risk use, and risky, at-risk, or hazardous use. Misuse and nonmedical use have a role when defined. Although "addictive potential" is likely a better term, "abuse potential" appears in the literature so readers need to be aware. "Opiate" refers to the naturally occurring compounds (e.g., morphine, codeine), and the term "opioid" includes opiates and the semisynthetic and synthetic compounds (e.g., heroin, fentanyl).

Terminology for Opioid Use Disorder

The International Society of Addiction Journal Editors (ISAJE) recommends not using stigmatizing terms, namely, "abuse" [12]. The ASAM's *Journal of Addiction Medicine* and others encourage the use of precise terms [13–16]. The U.S. Office of National Drug Control Policy has called for more accurate language [17]. "Addicted"

is a term to avoid because it is not clear if it refers to someone with the disease of addiction or if it refers to physical dependence. "Addicted baby" should always be avoided because babies cannot meet criteria for addiction (e.g., compulsive use despite knowledge of harm). Neonates can be physically dependent and have neonatal withdrawal (sometimes called neonatal abstinence syndrome, and more recently and preferably, neonatal opioid wihdrawal syndrome (NOWS) when due to opioids). In addition to "opioid use disorder," other accurate terms include "addiction" involving opioids, and DSM IV or ICD "dependence" (so long as it is clear it is a diagnosis and not a normal physiological state).

Implications of Terminology for Treatment

Use of inaccurate terms for the condition being treated causes confusion and can lead to ineffective treatment. For example, using the term dependence without specifying whether it is a diagnosis or a normal physiological state could lead to inappropriate care (one condition has an effective treatment, the other requires no treatment). Use of the term "abuse" is confusing because it does not distinguish use from a disorder, and use of "abuse" or "misuse" to describe a chronic condition can lead to conceptualizing treatments as short term or acute instead of long term and chronic as they should be. Furthermore, use of stigmatizing terms can negatively affect care quality [18–20]. When patients are described with the term "abuse" instead of "disorder," clinicians are more likely to recommend punitive approaches [18, 19]. Terms that define people entirely by their disease or behavior can be stigmatizing. Such terms include "abuser," "user," "addict," and "junkie." While some people with addiction call themselves "addicts," and this may even be helpful to their recovery (to recognize their condition) it may also reflect internalized stigma. For clinicians, it is better to use accurate, medically defined, and less stigmatizing person-first terminology (e.g., patient with "opioid use disorder" and not "addict"). Some patients will react negatively to disease-first terminology (e.g., "addict"), and accepting of a label has never been shown to be a requirement for successful treatment or recovery. Patients are people with diseases or disorders, in addition to families, jobs, and lives.

Medication (including opioid agonist) treatment for addiction has been labeled "medication-assisted," "substitution," or "replacement." Regardless of the implications of the terms (political correctness or policy), the labels are not accurate. Medication does not reproduce the effects of illicit heroin use, thus it is not a substitute or replacement. Medications do not "assist" treatment; they are treatment with proven efficacy in randomized trials that often fail to show additional benefit for other added treatments [21–25]. For example, when patients are treated with buprenorphine in clinical trials, and randomized to minimal or more intensive counseling, illicit opioid use decreases dramatically and persists while the medication is continued, but no differences in outcome are seen related to the intensity of counseling. Describing medication treatment as "using" medications or "drugs" is another way that such treatment is devalued. Instead, as with other conditions, people are "prescribed," "take," and "adhere to" "medications." Aside from inaccuracy, the impact of using inaccurate terms has implications for policy and access to treatment. If clinicians and

policymakers view medication as similar to using illicit drugs or as optional additional treatments, and not as efficacious medical treatments, access may be limited. In fact, this terminology may be a cause or at least a reflection of inaccurate perceptions of the efficacy and proper role of medication treatment for addiction.

Testing is often performed during treatment to assess patients for exposure to addictive drugs, licit and illicit. Unfortunately, test results are often presented or described as "dirty," and even the patients with addiction themselves are described as "dirty" or "clean." Again, although some people with addiction have adopted this terminology, it is likely that they have internalized the stigma and they use the terms because clinicians and others have encouraged them to do so. To the extent the terms help an individual, there is no recommendation to advise patients to change. But clinicians should record and present results like they do for other tests preferring terms such as "positive" and "negative" or "detected" and "not detected." Clinicians should describe people as "abstinent" or "in remission" or "in recovery," or as people using opioids (not as "users"), people not using opioids, or as people who have a current opioid use disorder [26]. The results of tests can also be described as indicating risk for return to use or disorder recurrence. "Relapse" as a term, although it may be favored and understood by many with addiction, is falling out of favor as it implies a (false) dichotomy [27]. The dichotomy implies that one relapses suddenly or does not relapse, at one instant of time, when in fact, people may begin to have recurrent symptoms that worsen over time and that a return to meeting criteria for an active or current disorder isn't simply attributable to a single return to use. "Detoxification" or "detox" is often used to refer to withholding illicit drugs and using medications and environment to ease symptoms of withdrawal. The term is a misnomer and instead should be called drug withdrawal (syndrome) or management of withdrawal. Locations that deliver "detoxification" can be referred to as acute treatment facilitities that deliver initial treatments, as entry points to care, induction or initiation centers.

Thus, terminology for treatment should include management of withdrawal, treatment, counseling, medication treatment, medication for addiction treatment, medication treatment for addiction, medication-based treatment, opioid agonist treatment, and even psychosocially assisted pharmacotherapy [28]. Testing should be described as it is described for other health conditions. Response to treatment should be described in terms of use, remission, and recurrence.

Conclusions

Language shapes policy and even influences individual treatment. Accurate, clearly defined, terms are critical for being able to identify and implement effective policies and treatments for opioid use disorder. Stigma can affect behavior but stigmatizing people to the extent they are entirely defined by a condition is not beneficial to anyone, nor is it respectful. Herein, I have recommended terminology for opioid use and opioid use disorder and its treatment that is accurate and also nonstigmatizing (Table 4.1). My recommendations are mainly for clinicians, scientists and policymakers, and not for people with addiction. Those suffering from opioid addiction can choose terms they find useful, though I expect that over time, just as is the case

Table 4.1 Recommended terminology for opioid use, disorder, and treatment and terms to avoid

Recommended terms	Terms to avoid
Unhealthy use	
Use, low-risk use, lower-risk use	
Risky, at-risk, hazardous use	Inappropriate use, abuse
Nonmedical use, misuse (when defined and referring to use without a prescription or beyond that prescribed)	Abuse, misuse as the sole term to describe disorder
Dose, use	Fix
Methadone, methamphetamine, methylphenidate	Meth
Addictive, addiction potential, addiction liability	Abuse potential, abusable
Addiction involving opioids, opioid use disorder, opioid dependence (ICD), harmful use (ICD)	Abuse, dependence without specifying physiologic vs. ICD or (former) DSM diagnosis
Person with disorder or addiction or physiological dependence, as the case may be	Addicted
Neonatal withdrawal, neonatal abstinence syndrome, neonatal opioid withdrawal syndrome	Addicted baby
Management of withdrawal, induction or initiation	Detoxification
Person with addiction, person who uses opioids, person with opioid use disorder	Addict, opioid user, opioid abuser, junkie
Medication, treatment, medication treatment, medication for addiction treatment (MAT), medication treatment of addiction, opioid agonist treatment	Substitution, replacement, medication-assisted treatment
Positive, negative, not detected	Dirty, clean
Remission, recurrence, return to use, use	Relapse

for "people with cancer," they too will prefer to be known as people who have addiction rather than "addicts." The use of stigmatizing, inaccurate, poorly defined terms for addiction and people suffering from it has likely impacted people with the condition, their families and friends, access to efficacious treatments, and has contributed to ineffective public policy. I anticipate that the use of clearly defined accurate nonstigmatizing terms, over time, will lead to clearer communication and better care and policy to address opioid use disorder and its treatment and prevention.

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Medication for the Treatment of Opioid Use Disorder

5

John A. Renner Jr. and Mitchell B. Crawford

Introduction

Following the American Civil War, physicians often prescribed long-term opioid pharmacotherapy for the treatment of opioid use disorder (OUD) [1]. Support for this practice declined at the end of the nineteenth century and was outlawed with the passage of the Harrison Act in 1914. This reflected the general mindset of the prohibition era that categorized alcohol and opioid use disorder as moral failings rather than medical problems. This shift in paradigm dominated medical thinking until the period following WWII when the medical community began to reclaim a role in the treatment of alcohol use disorder. The epidemics of heroin use disorder that followed WWII and the Vietnam War led to recognition of the failure of the criminal justice paradigm and to the search for a more effective public health and medical model for the management of OUD. The modern era of medication treatment for OUD began in 1972 with Food and Drug Administration (FDA) approval of methadone for withdrawal and maintenance treatment [2]. The restriction of access to the medication to heavily regulated "methadone clinics" reflected pervasive stigma, fear of contact with individuals with OUD, and the ambivalence of both the legal and the medical communities to the restoration of a medical model for managing OUD. In the ensuing 50 years, there has been a heightened need for treatment driven by new epidemics of addiction to prescription medications and more recently illicit fentanyl and growing awareness that OUD has become a signature public health crisis of our era. This has been matched by appreciation for the strong evidence base

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that supports long-term medication treatment as the most effective treatment for OUD. This chapter will review medication options for treating OUD and explain how medications fit into a comprehensive, multidisciplinary treatment approach to this ongoing public health crisis.

Treatment of Withdrawal

Medication withdrawal treatment for OUD involves treatment with a long-acting opioid medication and gradually tapering the dose at a rate that minimizes severe withdrawal and avoids excessive sedation or intoxication. The standard withdrawal medications are oral methadone or sublingual buprenorphine/naloxone (BUP/NX) [3, 4]. If patients refuse opioids, or if opioid medications are not available, the alpha-2-adrenergic agonist clonidine may be used. Clonidine moderates autonomic nervous system withdrawal symptoms but does not adequately control dysphoria, craving, insomnia, or restlessness. It is sometimes used in combination with methadone, to permit more rapid withdrawal treatment with lower doses of opioids. For most patients clonidine alone is not a satisfactory treatment for the full range of withdrawal symptoms; higher rates of relapse have been reported than those seen with other medications [5]. However, in patients being tapered in anticipation of induction on to extended-release naltrexone (XR-NTX), clonidine may permit more rapid induction and avoid the risk of precipitated opioid withdrawal [6]. An alternative alpha-2-adrenergic agonist, lofexidine, was approved by the FDA in 2018 for the treatment of opioid withdrawal. It is thought to have some safety advantages over clonidine since it produces less sedation and hypotension.

Withdrawal treatment begins with a complete drug and medical history, a complete physical examination, and urine toxicology. Even for patients on long-term BUP/NX or methadone treatment, it is difficult to accurately predict the patient's level of physical dependence. It can also be highly risky to estimate the quantity and quality of street drugs. Very potent analogues of fentanyl may be present, often in drugs purchased by unsuspecting patients. The only way to avoid an inadvertent overdose or precipitated withdrawal is to evaluate the patient for signs of moderate opioid withdrawal before initiating withdrawal treatment. This should be done using a standard withdrawal scale such as the Clinical Opiate Withdrawal Scale (COWS) or the Objective Opioid Withdrawal Scale (OOWS) [7, 8] and documenting the results in the patient's record. An initial dose of methadone 20 mg orally or BUP/NX 4/1 mg sublingually should not be administered until the patient scores in the mild to moderate range on the COWS or OOWS in an effort to mitigate the risk of overdose with administration of methadone and the risk of precipitated withdrawal with administration of BUP/NX (please see Fig. 5.2 and the associated description for further information). Lower initial doses of 10 mg methadone or 2/0.5 mg BUP/NX are recommended for younger patients or for individuals who have been using smaller amounts. For patients being transferred from maintenance programs, the clinician must always verify the dose and time of the last dose, before initiating any new medication.

Further dosing should be guided by the patient's response as indicated on the COWS/OOWS. An additional dose can be administered in 2–4 hours if withdrawal symptoms increase or do not subside. If the initial dose was effective in controlling withdrawal, it should be repeated in 12 hours if needed. Ordinarily the total dose in the first 24 hours of methadone should not exceed 40 mg or 16/4 mg BUP/NX except for clinically indicated exceptions. Once withdrawal symptoms are adequately controlled, the dose can be tapered at a rate that prevents further withdrawal and minimizes distress. Methadone can be reduced at a rate of 5 mg/day (or a maximum 20% dose reduction/day). An inpatient methadone taper can usually be completed in 5–7 days [9]. BUP/NX can be tapered at the rate of 50%/day. A more gradual taper extending over 13 days had a better outcome and was significantly more effective than clonidine [10, 11]. One study compared withdrawal treatment utilizing clonidine, methadone, and BUP/NX [5]. Compared with clonidine, BUP/NX patients were more likely to complete treatment, stayed in treatment longer (particular in outpatient withdrawal treatment), and had fewer withdrawal symptoms [11]. The outcomes showed no significant difference comparing methadone to BUP/NX in completion of treatment or severity of withdrawal, but withdrawal symptoms resolved more quickly in BUP/NX-treated patients.

The long-term outcome of withdrawal treatment is rarely good [12, 13]. There is a relapse rate of 80–93% within 1 year following a brief inpatient taper. The best results have been seen with very prolonged outpatient tapers or 1–2 week inpatient tapers followed by long-term residential treatment. Better results are seen with multiyear maintenance treatment followed by a very gradual outpatient taper. Nonetheless, even very stable patients have shown a relapse rate of 80% within 1 year following a taper [13]. Patients must be warned about these risks if withdrawal treatment is not followed by long-term residential care or treatment with XR-NTX. Large data sets have shown an elevated risk for fatal overdose immediately following inpatient withdrawal treatment or following termination of long-term treatment with methadone or BUP/NX [14]. All patients must be made aware of these risks.

New protocols are under study utilizing rapid inpatient clonidine taper combined with an escalating dose of naltrexone leading to induction on to XR-NTX. In some protocols, naltrexone is used to precipitate withdrawal, and then increasing doses of clonidine are used to suppress withdrawal symptoms as naltrexone is quickly increased to antagonist maintenance levels [15, 16]. These protocols often require initiation with very low doses of naltrexone that are not available formulations. Clinicians continue to seek out effective models for inducing physically dependent patients on to XR-NTX. Recent research has showed comparable efficacy between BUP/NX and XR-NX, once the patient has been stabilized on either medication (see below) [17]. However, long-term retention in treatment remains an issue in standard clinical practice [18].

Recently, efforts have been made to incorporate non-pharmacological interventions in the treatment of acute withdrawal. One such example is a percutaneous electrical nerve field stimulation device which received FDA approval for the treatment of opioid withdrawal in late 2017 [19]. The device is placed on the external ear for 5 days to stimulate neurovascular bundles with the purpose of helping to

alleviate symptoms of acute opioid withdrawal. The approval for this device was based on a small, uncontrolled, retrospective study which included 73 patients who saw a reduction in COWS scores from a baseline mean of 20.1 to 7.5 after 20 minutes, 4.0 after 30 minutes, and finally 3.1 after 60 minutes of wearing the device. It was also noted that of the 73 patient cohort, 64 patients transitioned to naltrexone after a 5-day course with the stimulation device [20]. There is limited evidence at this time for the role of non-pharmacological interventions in the treatment of acute opioid withdrawal; however, further study is needed.

In summary, it must be stressed that regardless of the medication or protocol used, medication withdrawal treatment for OUD has a poor outcome with more than 90% of patients relapsing within 1 year. All of these patients are at high risk for a fatal overdose. Unless withdrawal treatment is followed by long-term residential care (9 months or more), it should not be considered adequate treatment for OUD.

Maintenance Treatment

There is abundant evidence that long-term medication is the treatment of choice for most individuals with OUD [12, 17, 21, 22]. FDA-approved medications include the mu-opioid agonists methadone and buprenorphine or the antagonist, naltrexone. These treatment options have unique sets of advantages and disadvantages which need to be weighed for each patient individually.

Agonist Therapy

Any discussion of agonist therapy needs to first clarify what it is not; it is not a substitution of "one addiction for another." Agonist therapy for OUD is the use of a long acting medication (either methadone or buprenorphine) as a daily medication to induce opioid tolerance and prevent opioid withdrawal and craving. This mode of therapy has been demonstrated to establish physiologic stability, improve general health and nutrition, decrease injection drug use, decrease criminal behavior, increase employment, and stabilize lifestyle [13]. Individuals who have responded well to these medications no longer present the behavioral symptoms associated with an OUD and no longer meet diagnostic criteria for opioid use disorder.

Buprenorphine

Buprenorphine, a partial agonist at the mu-opioid receptor, was approved by the FDA for the treatment of OUD in 2002. Safety and efficacy have been shown in a number of double-blind, placebo-controlled clinical trials [23–26]. It has a very high affinity for the mu-opioid receptor and it will displace other agonists (either natural opiates or synthetic or semisynthetic opioids) from the receptor. However, as a partial-agonist, it does not fully activate the receptor. This "ceiling effect" prevents respiratory depression regardless of the amount ingested, making buprenorphine an unusually safe medication (Fig. 5.1). Because of its safety and its slow dissociation

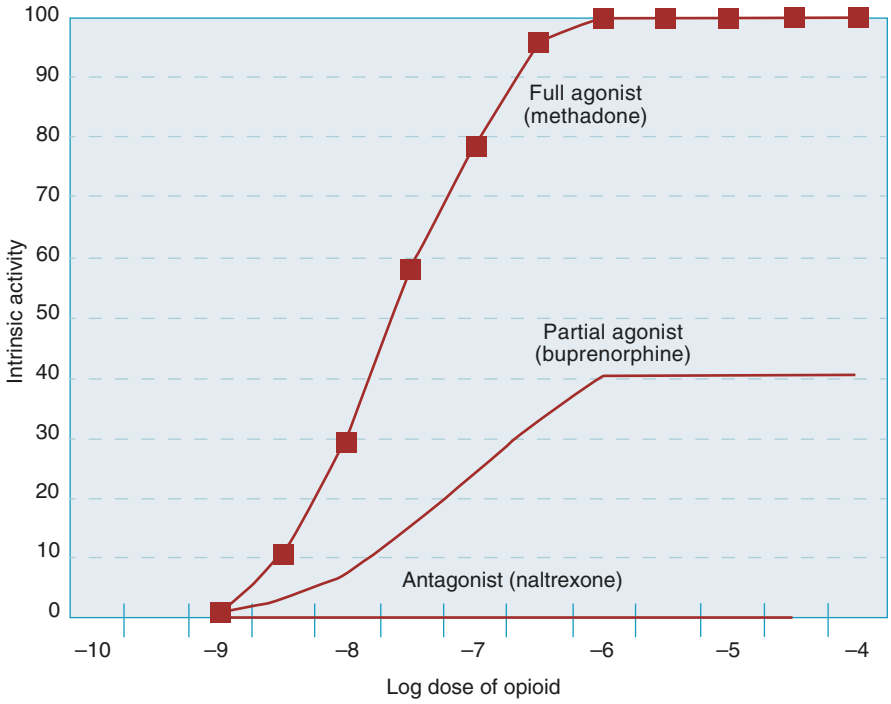

Fig. 5.1 Intrinsic activity of OUD medications. (Adapted from the Treatment Improvement Protocol 63 from the Substance Abuse and Mental Health Services Administration [62])

from the receptor, it provides long lasting receptor blockade, making it an ideal choice for the treatment of OUD.

This Schedule III medication is available as either a single medication (mono-formulation) or in combination with the antagonist naloxone (combo-formulation) in a ratio of approximately 4 mg buprenorphine to 1 mg naloxone. The combo-formulation was developed for sublingual use, to discourage diversion and misuse. Because naloxone has poor sublingual bioavailability, it has no clinical effect when taken as prescribed ensuring that the patient receives the full, intended buprenorphine effect. However, should the combo-formulation be crushed and injected, the naloxone is active, either blunting the effect of the buprenorphine or precipitating full opioid withdrawal in physically dependent individuals. Buprenorphine is now available in sublingual or buccal formulations, as a 6-month implantable rod, or as a monthly subcutaneous injection. Available branded or generic formulations (in some cases, tablets or film strips) include sublingual formulations, either alone (Subutex®) or in a combination formulation with naloxone (Bunavail®, Suboxone®, and Zubsolv®), a 6-month implant (Probuphine®), and a monthly injectable (Sublocade®).

Because of its combination of clinical efficacy, safety, and lesser diversion potential, the FDA and the Drug Enforcement Administration (DEA) approved

buprenorphine for the treatment of OUD in the office-based setting without the regulatory constraints placed on methadone treatment. The introduction of office-based treatment for OUD has been a major public health success [27]. Patients have been attracted to the greater flexibility of office-based treatment and the faster induction on to buprenorphine, as compared to methadone. Methadone, however, has higher retention rates and may be a better option for patients who require closer monitoring and a broader range of ancillary services. It is recommended that all maintenance patients be engaged in individualized psychosocial supports, which can be delivered by patients' healthcare providers in the form of medication management and supportive counseling and/or through adjunctive addiction counseling, recovery coaching, mental health services, and ancillary supports that may be necessary (TIP 63 from SAMHSA).

The DATA 2000 legislation indicated that to qualify for buprenorphine treatment, an individual must be 16 years of age and meet the DSM-IV criteria for opioid dependence. This is currently interpreted as meeting *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition criteria for OUD, moderate or severe. As compared to methadone regulations, this permits the treatment of younger people with shorter addiction histories. Initial data from buprenorphine treatment found that patients who were younger, white, primarily used prescription opioids, and had greater stability were more likely to utilize buprenorphine treatment. More recently, evidence has demonstrated the effectiveness of buprenorphine in more marginalized and complex patient populations, including people recently incarcerated, people experiencing homelessness, people who inject opioids, and patients engaging in lower threshold settings (see, e.g., [28–31]).

Obtaining the DEA Buprenorphine Waiver

DATA 2000 legislation specified a number of ways for a physician to obtain the waiver to prescribe buprenorphine. Individuals could apply if they were certified in addiction psychiatry by the American Board of Psychiatry and Neurology, or certified in addiction medicine by the American Board of Addiction Medicine, or if they completed an 8-hour training course. The clinician's patient load is capped to 30 for the first year. After holding a waiver for 1 year, clinicians can apply for an increase to treat up to 100 patients. The Comprehensive Addiction and Recovery Act of 2016 (CARA) legislation and Substance Abuse and Mental Health Services Administration (SAMHSA) regulations of 2016 now permit certain clinicians to apply for an increased waiver limit of 275 patients after 1 year at the 100 patient limit [32, 33]. These regulations also permit nurse practitioners and physician assistants to apply for the waiver, but they are required to complete 24 hours of training. By 2017, more than 35,000 physicians had obtained the DEA waiver to prescribe buprenorphine. Of those physicians with the waiver, 23,982 can prescribe for up to 30 patients, 9285 for up to 100 patients, and 2525 for up to 275 patients. It is estimated that there are now over 600,000 patients being treated in the office-based setting, and an additional 12,500 receiving buprenorphine in opioid treatment programs, compared with 350,000 patients on methadone maintenance.

Clinical Use of Buprenorphine

Initiating buprenorphine treatment requires a clear understanding of the drug's pharmacology. As a partial opioid agonist, it has a very high affinity for the mu-opioid receptor, and it will displace most other opioid agonists. Because it does not fully activate the receptor, any individual physically dependent on a full opioid agonist will experience this displacement as the acute onset or severe worsening of opioid withdrawal symptoms, a syndrome called "precipitated withdrawal." This severe but brief syndrome is comparable to the effects of treatment with an opioid antagonist. The important clinical task of buprenorphine induction is to introduce the medication while not causing precipitated withdrawal. This problem can be avoided by waiting until the patient is opioid free or already in mild to moderate opioid withdrawal before administering the first dose of buprenorphine. This is best accomplished by instructing the patient to avoid any opioids for 12–24 hours for short acting opioids and at least 24 hours for long acting opioids prior to induction and by documenting the presence of withdrawal using a standard scale such at the COWS. The COWS scores patients on observable measures including pulse, sweating, restlessness, pupil size, tremor, yawning, runny nose/tearing, and goose flesh and more subjective measures such as bone or joint aches and abdominal cramps, permitting a reliable measure of the severity of withdrawal (Fig. 5.2) [8].

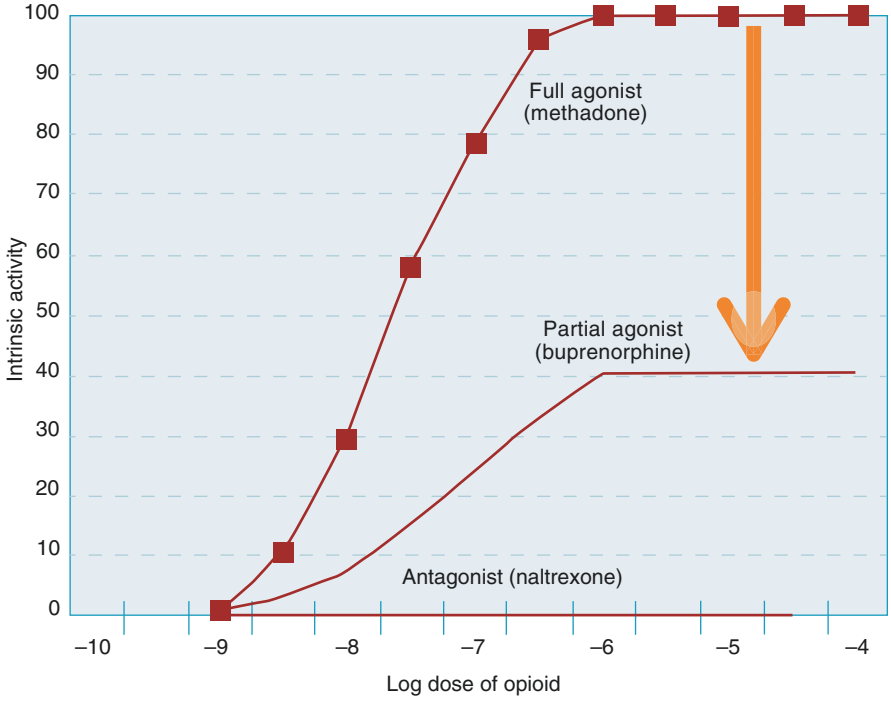

Fig. 5.2 Precipitated withdrawal if buprenorphine displaces full agonist conceptual representation only, not to be used for dosing purposes. (Adapted from the Treatment Improvement Protocol 63 from the Substance Abuse and Mental Health Services Administration [62])

To avoid precipitated withdrawal, the patient should demonstrate mild to moderate opioid withdrawal (>12) on the COWS before he or she takes the first buprenorphine dose. If the patient has been using a more potent opioid such as fentanyl, we recommended that induction not begin until they have demonstrated a higher level of withdrawal in the range of 13–15 on the COWS. In observed induction, an initial dose of BUP/NX 2/0.5 mg or BUP/NX 4/1 mg sublingually is given under observation and the patient is observed for an additional 1+ hours to ensure that there is no precipitated withdrawal. Supplemental doses can be given if withdrawal symptoms persist, with a maximum recommended first-day dose of BUP/NX of 16/4 mg.

Home induction, or unobserved induction, is an alternative option which has been demonstrated to be non-inferior to observed induction [34]. A home induction involves giving a patient an initial prescription for BUP/NX to take up to 16/4 mg on day one with careful instructions on the induction process. These patients can be monitored daily by telephone to ensure a safe and effective induction and seen for close follow-up in the office. The dose can be increased in 2–4 mg increments over the next 2–3 days to a dose that eliminates any further craving or withdrawal symptoms. The target maintenance dose was initially thought to be between 12 and 16 mg BUP/NX sublingually daily; however increasing evidence has demonstrated that higher doses (16–32 mg) are associated with improved treatment retention [35, 36]. Additional dose increases may be considered if craving and opioid use does not cease or diminish within 1–3 weeks.

In some circumstances it may be appropriate to initiate buprenorphine treatment in individuals not currently physically dependent (individuals recently released from residential care or from the justice system). Toxicology testing should be obtained to document their opioid negative status. Dosing should begin with BUP/NX 2/0.5 mg sublingually the first day and increase by 2/0.5 mg daily until a stabilization dose is achieved. If the patient experiences any level of sedation or intoxication, the dose should be reduced or further increases held until there is no further evidence of intoxication.

Buprenorphine has a long half-life, and clinicians should wait 5–7 days after initial stabilization or after any further dose increases to assess the full clinical response. The FDA-approved dosing range is 4–24 mg. Studies on receptor occupancy suggest that there is little pharmacological justification for doses over 32 mg [37]. The implant formulation was approved in 2016 and is only recommended for stable patients currently on a sublingual BUP/NX dose of 8/2 mg [38]. Additionally, the monthly injectable buprenorphine depot formulation was approved in 2017 which provides greater flexibility in dosage when compared to the implant formulation. As with the implant formulation, before transitioning to the depot formulation the patient must have been on a stable dose of transmucosal buprenorphine. The depot requirements differ in that the transmucosal dose could be between 8 and 24 mg as long as the dose has been stable for at least 7 days before initiating the depot formulation. Furthermore, after the first 2 months of 300 mg depot injections, the dose of the injection decreases to 100 mg, but the dose can be titrated back up to 300 mg if clinically indicated [39].

Weekly office visits are generally recommended for the first 3–4 weeks, with a gradual increase in duration between appointments as clinically indicated. Frequent monitoring visits and regular toxicology testing are associated with the best outcomes. As such, even very stable patients should generally be seen once every 1–2 months.

Patients treated with buprenorphine can benefit from individualized psychosocial supports. These can range from medication management and supportive counseling offered by the patients' provider to more intensive adjunctive group or individual counseling, ancillary services, and mutual support (TIP 63 SAMHSA). Patients with significant co-occurring psychiatric problems may do best with adjunctive counseling. There have been four studies in both primary care and mental health settings that have shown that more stable patients may do just as well with less intensive ancillary services. Medication management with supportive counseling in the setting of a prescriber visit has been demonstrated to be an effective management tool for selected patients with no serious co-occurring medical or psychiatric disorders. The patients were seen either weekly or monthly for 15–25-minute individual visits. The clinician would monitor adherence, response to treatment, and any adverse effects. They would also provide education about alcohol use disorder/OUD, health consequences, and treatments, encourage abstinence from illicit opioids and other addictive substances and participation in community supports for recovery, and encourage other lifestyle changes that support recovery [12, 40–42]. The World Health Organization recommends that all patients with OUD be offered psychosocial interventions with buprenorphine but that people who decline additional counseling should not be denied medication treatment [43].

Buprenorphine has also shown promise as a treatment for pregnant women with OUD. The "MOTHER" study was a double-blind, double-dummy randomized control trial of buprenorphine versus methadone for pregnant women. The results showed comparable safety and equivalent reductions of illicit opioids and other substance use with both medications. There were higher dropouts in the buprenorphine condition but higher rates of medical complications at delivery in the methadone condition. Of particular note were the milder withdrawal symptoms seen in infants born to the mothers on buprenorphine [44, 45]. It is anticipated that buprenorphine will soon become accepted as standard care for pregnant women with opioid use disorder. For women who become pregnant while being treated with buprenorphine, it is recommended that they be transferred from the BUP/NX combo-formulation to the mono-formulation and that they be referred for prenatal care while being continued on buprenorphine [46].

There is little information available on the interaction of buprenorphine and other medications. Like methadone it is a substrate of cytochrome P450(CYP)3A4, but unlike methadone, it has an active metabolite, norbuprenorphine, which appears to moderate the effect of other drugs that may induce buprenorphine metabolism. Drugs that inhibit CYP3A4, such as nefazodone or fluoxetine, could theoretically cause problems, but little difficulty has been reported. Of greater concern is the pharmacodynamic interaction between buprenorphine and sedating drugs such as benzodiazepines and antihistamines. Buprenorphine should be used with caution in

patients with active, severe benzodiazepine use disorder, although the risks are less than among people treated with methadone and misusing benzodiazepines [47]. Overall, buprenorphine has fewer drug-drug interactions than methadone and can be prescribed more easily to a broader range of patients.

Methadone

Methadone was the first medication approved by the FDA for maintenance treatment of OUD. It acts as a full agonist at the mu-opioid receptors as well as an *N*-methyl-*D*-aspartate receptor antagonist. Treatment with methadone along with supportive services is highly effective as a maintenance treatment, with those in treatment for 6 months showing a substantial decrease in illicit opioid use. Treatment retention is higher with methadone maintenance compared to prolonged and psychosocially enriched withdrawal management [48], and opioid use is lower among those treated with methadone compared to other types of addiction treatment [49]. Ball and Ross noted that there was a nearly 80% decrease in crimes committed by patients after successful treatment in the methadone clinic [13]. Additionally, when comparing individuals engaged in illicit opioid use to those on long-term methadone maintenance, there remains some endocrine dysfunction such as hypogonadism in both groups, but there also appears to be an allostasis that occurs with long-term methadone use which stabilizes some endocrine physiology. This stabilization is most notable in the hypothalamic-pituitary-adrenal axis [10].

The use of methadone is strictly regulated in the United States and only available to patients for the treatment of OUD in designated treatment programs. Specific guidelines that were established in Title 42 of the Code of Federal Regulations (42 CFR) require that patients must be 18 years of age and older and have a documented 1-year history of addiction to opioids prior to treatment. According to 42 CFR patients less than 18 years of age can be treated with methadone with parental or guardian consent, if they have had two documented previous treatment attempts in the previous 12-month period. Additionally, it is possible to waive the 1-year history of OUD for patients previously treated with methadone, patients who are pregnant, or for patients within 6 months of incarceration. There are two exceptions when methadone can be prescribed for the treatment of OUD outside of a designated treatment program. These exceptions are (1) during emergent care (such as in the emergency department, for no longer than a period of 3 days) and (2) while receiving care as an inpatient for a medical or psychiatric condition other than addiction treatment [50].

Methadone Induction

In contrast to buprenorphine, methadone is a full mu-opioid agonist which does not display the ceiling effect seen in buprenorphine in regard to respiratory depression. This is an important consideration when initiating methadone treatment and when evaluating other medications that are concomitantly being prescribed, such as benzodiazepines. Methadone has a long half-life of 8–59 hours and an analgesic effect lasting about 4–8 hours. The respiratory depressant effects of methadone peak later and last longer than the analgesic effects, so great care must be taken in titration. Fatal overdoses have occurred if the dose is increased too quickly, most frequently seen when

methadone is prescribed for pain rather than by an opioid treatment program for addiction. Unlike with buprenorphine there is no risk of precipitated withdrawal with methadone, so it is not necessary that a person be in withdrawal when initiating treatment. Generally, in opioid treatment settings, dosing is initiated when withdrawal symptoms are present to confirm the presence of physiological dependence; however individuals who have not been recently using opioids but are at high risk of relapse such as those released from incarceration should still be initiated in treatment at a lower initial dose. Federal regulations limit the initial oral induction dose to 30 mg, and the total first day dose to a maximum of 40 mg. The next daily dose may be increased to a maximum of 50 mg if withdrawal symptoms are still present. During subsequent days, the dosage increase should not be greater than 10 mg per week as it is important to reach a steady-state concentration before escalating to avoid potentially toxic dose accumulation [51]. The target dose range for most patients is 80–100 mg which should eliminate craving and illicit opioid use. Doses may be titrated up or down based on clinical effect. There is tremendous individual variation in methadone pharmacokinetics, and some patients may require much higher dosages [52].

Methadone is metabolized in the liver by CYP3A4, CYP2D6, and possibly also CYP1A2. However, the majority of the N-demethylation of methadone to an inactive metabolite is done by CYP3A4, and the great variability of this isoenzyme seems to relate to the large range of half-life in individuals. Caution should be taken when evaluating concurrent medications that are known to induce or inhibit these enzymes of metabolism, as well as in patients with hepatic insufficiency [52]. There has also been some concern about the effects of consumption of grapefruit juice on plasma levels of methadone, which has been shown to have a modest effect with an increased bioavailability of methadone [53]. Constipation is a common side effect, and consideration should be given to prescribing a bowel regimen in addition to methadone. Drug-drug interactions can be expected with methadone, and many of the medications are used to treat HIV/AIDS, seizure disorders, and tuberculosis.

Lastly, there is a boxed warning with methadone for the potential to cause a prolonged QTc interval and serious arrhythmias, such as torsades de pointes. This is particularly noteworthy in patients on doses of methadone over 100 mg and should be taken into consideration in any patient with a history of syncope, a cardiac history, or a familial long QT. In patients at risk, it would be appropriate to monitor the QTc interval with an electrocardiogram prior to initiating treatment and during treatment at a frequency that is appropriate for each patient's individual risk.

Methadone is currently regarded as the "gold-standard" for pharmacological treatment of OUD during pregnancy. Fetal outcomes are improved when the mother is engaged in a methadone treatment program. Breastfeeding should be encouraged while taking methadone, as long as there are no contraindications noted. Although there are case reports of sedation and respiratory depression in some nursing infants, there is poor correlation between maternal methadone dose and infant symptomatology. In addition, concentrations of methadone in breast milk are low supporting the American Academy of Pediatrics recommendation to breastfeed regardless of methadone dose [54]. Despite the known benefit of breastfeeding among women treated with

methadone, there continues to be a lack of support from the healthcare community and misinformation which present significant barriers to breastfeeding success [55].

Antagonist Therapy

Naltrexone

The only opioid antagonist that is FDA approved for maintenance therapy is naltrexone, which acts as a competitive antagonist at the mu-opioid receptor with long-lasting effects (generally about 24 hours per oral dose). In most patients, compliance with the oral formulation has been very poor. Efficacy for the treatment of OUD with the daily oral formulation has been better for patients in a formal and supervised setting, such as court ordered programs or physician monitoring programs, where adherence can be monitored. For the general population, compliance with the oral formulation is a problem, and it is strongly recommended that patients be prescribed the extended-release formulation of naltrexone (XR-NTX) which is given by intramuscular injection every 28 days. Prior to initiation of either the oral or XR-NTX medication, toxicology should be performed as naltrexone will precipitate opioid withdrawal if any amount of exogenous opioid is present. The patient must be abstinent from opioids for 7–10 days prior to induction.

A naloxone challenge test is recommended in patients when there is concern for precipitating withdrawal. This test involves giving a dose of naloxone to a patient when there are no longer any signs or symptoms of opioid withdrawal, and monitoring their response for 1 hour. If the naloxone precipitates signs or symptoms of opioid withdrawal, this should be relatively short lived due to the short half-life of naloxone. Naltrexone should not be initiated until there is no evidence of risk for precipitating withdrawal. Liver function testing should also be done prior to initiation and during treatment for monitoring, as naltrexone can rarely be hepatotoxic. It is often clinically determined that the benefit of the medication outweighs the risk of hepatotoxicity in cases of mild transaminitis, but it is contraindicated to use naltrexone if the patient is in liver failure [56].

A frequent barrier to success with XR-NTX is the induction process, since many patients are unable to achieve the required 7–10 days of abstinence prior to initiation of the medication. There have been several protocols developed to address this problem, as described above in the section on the treatment of withdrawal, such as very low dose naltrexone introduced orally and titrated up over 7 days to the daily dose of 50 mg at which point the patient can be transitioned to the XR-NTX [6]. With this approach it is anticipated that more patients would be induced on to XR-NTX. The efficacy of XR-NTX has been studied in comparison to sublingual buprenorphine. In intention-to-treat analysis, buprenorphine was superior to naltrexone with relapse detected in a greater percentage of XR-NTX-treated patients than buprenorphine-treated patients (65% compared to 57%). There was no statistically significant difference in outcomes in the two groups when comparing only those who were successfully induced on to either medication, but 28% of the XR-NTX group was not able to successfully complete induction, as compared to

6% of the buprenorphine group [18, 57]. Clinically, the use of XR-NTX is likely the best choice for patients in the following categories: those who are highly motivated, are unable to receive agonist treatment (due to availability or employment restrictions), and those who are able to complete medically supervised withdrawal to get to successful XR-NTX initiation.

Diversion Control

When prescribing any medication, the clinician must determine whether or not the risk is outweighed by the benefit. In the case of controlled substances, an important consideration when calculating risk is whether or not the medication is being used as prescribed. The CARA legislation required that clinicians develop a diversion plan to reduce diversion in their practice [33]. This must be reviewed periodically with their patients. Aside from misuse of the controlled substances, prescribers must also be alert to warning signs that the medication is being diverted. Clinically, toxicology can be a helpful tool to help monitor whether or not the substance is being ingested by the patient and if there are concurrent illicit or non-prescribed substances being used. It is important to coordinate with the testing laboratory to determine which substances are detectable in each assay, as a typical "opioid screen" may not include substances such as fentanyl or buprenorphine, or other opioid pharmaceuticals. Confirmation testing is also recommended if applicable, as the screening assays are often designed to have a high sensitivity, which can produce a relatively high percentage of false positives. The use of pill counts may also be implemented, with the patient being randomly requested to present between scheduled clinic visits to monitor whether an appropriate amount of medication remains.

Another important tool is the utilization of prescription drug monitoring programs (PDMPs). PDMPs are state specific databases that can be searched by prescribers to receive a report of the recent prescriptions of controlled substances in that respective state. More recently, state PDMPs have been sharing data so that prescribers can query results from other states in addition to their own. A meta-analysis of studies on the overall impact of PDMPs on overdose showed insufficient evidence, with some studies demonstrating reduced overdoses and others showing an increase in heroin-related deaths [58].

Non-pharmacological Treatment

There has been some recent interest in the use of non-pharmacological interventions for the treatment of substance use disorders. Primarily, research is occurring to establish whether or not there is a role for deep brain stimulation (DBS) as well as repeated transcranial magnetic stimulation (rTMS). The current focus of rTMS studies has been addiction to nicotine, alcohol, and stimulants, with most focusing on nicotine. Furthermore, there have been a few case reports of the use of DBS showing some potentially limited effects in decreasing use of opioids. The number

of patients in the case reports for DBS is very low and the procedure is invasive, requiring placement of the electrode by neurosurgery. There is insufficient evidence to recommend use of these treatments at this time.

Treatment of Opioid Overdose

All patients with OUD should receive education about opioid overdose prevention and should be prescribed a naloxone rescue kit. Particularly, those who have recently completed medical withdrawal treatment or have been abstinent from opioids for a significant period of time should be warned about the loss of tolerance and increased risk of overdose if they resume the use of opioids. It would also be wise to provide overdose prevention education to patients who misuse illicit substances other than opioids, such as stimulants, designer drugs, or counterfeit medications, as these may be prepared in facilities that also process fentanyl and could be contaminated with this potent opioid.

When approaching an unconscious person who is not breathing, the possibility of opioid poisoning should be high on the differential. Signs of opioid poisoning are respiratory depression, cyanosis, miosis (with the exception of poisoning with meperidine), and a limp body. Initial management is to dial 911 and to ask for help from bystanders, specifically requesting an automated external defibrillator (AED) and naloxone. After determining that the environment is safe to intervene physically, initiate cardiopulmonary necessitation (CPR) until either an AED or naloxone arrives, at which point CPR should pause to utilize these aids. Naloxone should be used immediately whenever available, via intranasal or intramuscular delivery. Repeated doses of naloxone may be required. If there is no response to naloxone even after repeated dosages, continue CPR and use the AED until additional help arrives. If there is a response to naloxone, continue to monitor and provide appropriate care as indicated until additional help arrives. It is necessary to warn patients that the effect of naloxone is short-lived, and if the opioid ingested has a longer half-life than naloxone, respiratory depression could resume without subsequent treatment. When providing care after an overdose, a thorough evaluation for safety should occur to help determine whether it was an accidental poisoning or a suicide attempt. All overdose patients should be referred for treatment for a substance use disorder. At the very least, there should be a referral placed for mental health services following acute treatment [59].

The introduction of intranasal naloxone was correlated with a rapid and drastic decrease in the amount of heroin-related deaths shown in data from the San Francisco Medical Examiner's reports from 1993 to 2010 [60]. Despite this strong evidence of utility, concerns have been raised about the potential legal implications of providing medical care in an overdose scenario. As such, most states, but not all, have Good Samaritan laws in place to help promote intervention. It is recommended that each provider be aware of the laws specific to the state in which they practice.

Additional Considerations

Acute Pain

When patients with OUD are experiencing acute pain, special care must be taken when providing treatment. Single daily doses of methadone or buprenorphine do not provide 24-hour analgesia. Mild to moderate acute pain can usually be managed with the addition of non-opioid analgesics such as nonsteroidal anti-inflammatory drugs (NSAID) to the daily maintenance medication. If that is not adequate, the daily buprenorphine dose can be divided to provide better analgesia and supplemented with an additional 2/0.5 mg BUP/NX as needed for breakthrough pain. In methadone patients, their daily maintenance dose can be supplemented with an additional 10 mg methadone or another full agonist as needed. In cases of severe pain in patients receiving agonist treatment with buprenorphine, supplemental doses of a full agonist may be added, or it may be necessary to transition from buprenorphine to a full agonist to provide necessary analgesia and then re-induce buprenorphine after the pain subsides [TIP 63 from SAMHSA]. For the management of the pain associated with childbirth, the mother should continue on her normal maintenance dose of methadone or buprenorphine and then should also be treated with standard of care acute pain management options.

If a patient on opioid antagonist treatment experiences acute pain, it may be necessary to involve anesthesia to administer agents such as ketamine or to utilize high doses of fentanyl or buprenorphine to override the naltrexone blockade. As with any patient, caution should be taken to prescribe opioid medications only when clinically appropriate. Alternatives to opioids such as NSAIDs and nerve blocks should be considered whenever appropriate.

Concurrent OUD and Other Mental Illness

It is not uncommon to encounter OUD in patients also diagnosed with additional mental health disorders. Data from the National Survey on Drug Use and Health examining patients aged 18 and older from 2008 to 2014 estimated that of the 20.2 million diagnosed with a substance use disorder, 7.9 million also had additional mental health diagnoses. When treating these “dual-diagnosis” patients, it is important to coordinate care with all members of the treatment team and carefully consider medication choices. Medications with misuse potential, especially those that have profiles of having a rapid onset and a short half-life, such as some benzodiazepines, should be avoided [61]. Otherwise, patients on any of the approved medications for OUD will respond to the standard pharmacotherapies and psychological interventions for other mental health disorders. Methadone metabolism maybe altered by some of the psychiatric drugs metabolized by the CYP3A4 system; this is not an issue for naltrexone or buprenorphine.

Integrating Medication Treatment into a Comprehensive Recovery Program for OUD

Research has shown that long-term medication treatment for OUD is an essential element of recovery and that short-term treatment providing only medically supervised withdrawal is rarely an effective strategy [62]. Nonetheless, most patients will also benefit from a full range of psychosocial services to support stable recovery. Structured individual or group counseling based on cognitive behavioral models has the best evidence for efficacy, though patients should also be encouraged to participate in mutual support programs which are highly associated with long-term recovery. For patients on methadone or buprenorphine, participation in Alcoholics Anonymous (AA) may be more beneficial than Narcotics Anonymous (NA) since the AA fellowship is more accepting of patients on medication. Alternative mutual help organizations such as SMART Recovery are also more accepting of medication treatments, although evidence for recovery-related benefits specifically from SMART Recovery participation is limited. Whenever possible, families should also be engaged in the treatment process. Finally, and equally important, all patients with OUD should be screened for co-occurring psychiatric disorders. Given the high prevalence of co-occurring disorder, identifying psychiatric illness and offering concurrent treatment are crucial. Recovery is unlikely unless these conditions are also treated. It is useful to consider medication for OUD as a platform for recovery. It is necessary to support recovery, but patients should also have access to a full range of addiction services to promote successful recovery. While access to comprehensive psychosocial services must be available to all, designing systems which mandate participation may limit access for certain marginalized patient populations. By contrast, lower threshold treatment models which make medication readily accessible in conjunction with voluntary participation in comprehensive services that meet the needs of the individual patient are more likely to create the broad access that is needed to ensure the greatest number of individuals with OUD is able to get lifesaving treatment.

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Psychosocial Approaches in the Treatment of Opioid Use Disorders

6

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Abbreviations List

AA	Alcoholics Anonymous
ACT	Acceptance and commitment therapy
AUD	Alcohol use disorder
BI	Brief intervention
CBT	Cognitive-behavioral therapies
CM	Contingency management
DSM	Diagnostic and statistical manual of mental disorders
IOPs	Intensive outpatient programs
MASH	Massachusetts Association of Sober Housing
MHOs	Mutual-help organizations
MI	Motivational interviewing
MM	Medication management

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NA	Narcotics Anonymous
NARR	National Association for Recovery Residences
OUD	Opioid use disorder
PHPs	Partial hospital programs
RCTs	Randomized controlled trials
SAMHSA	Substance Abuse and Mental Health Services Administration
SBIRT	Screening, brief intervention, and referral to treatment
SUD	Substance use disorder
TAU	Treatment as usual
TES	Therapeutic Education System
TSF	Twelve (12)-step facilitation

Introduction

Admissions to substance use disorder (SUD) treatment for individuals with a primary opioid problem have increased dramatically over the past decade in the United States. Individuals with an opioid use disorder (OUD) may present to treatment for their use of heroin or other opioids, including prescription opioids for pain (e.g., oxycodone) [1]. The proportion of individuals aged 12 and older admitted to SUD treatment with a primary heroin problem doubled from 2005 (14%) to 2015 (26%), and the proportion of treatment admissions for individuals reporting other primary opioid problems similarly doubled from 2005 (4%) to 2015 (8%) [1].

Pharmacological treatments for OUD, including opioid agonists like buprenorphine (often prescribed as buprenorphine/naloxone) and methadone, and opioid antagonists like the extended-release injection formulation of naltrexone, have been shown to decrease rates of opioid use and the likelihood of opioid overdose [2, 3]. For example, in large treatment samples, opioid agonist treatments are associated with 50% reductions in the odds of overdose death [2, 4]. Given their clinical efficacy and cost-effectiveness, many experts and, correspondingly, clinical practice guidelines regard opioid agonists—and antagonists for those who can complete medically supervised withdrawal—as first-line treatments for OUD [5, 6].

There is a broad consensus that an adequate public health response to the current OUD landscape depends on increased access to empirically supported pharmacological treatments [7, 8]; at the same time, psychosocial interventions maintain an integral role in OUD treatment for several reasons. First, national guidelines from major clinical practice organizations, including the American Society of Addiction Medicine [5, 9] and the American Psychiatric Association [10], as well as from federal programs such as the Substance Abuse and Mental Health Services Administration (SAMHSA) [11–13] and the Department of Veteran's Affairs [14], recommend that psychosocial services be delivered alongside pharmacotherapy. Furthermore, physicians who provide OUD medications are required to offer psychosocial services, either in their own practices or through

referrals to reputable behavioral health practitioners in their communities, in accordance with the Drug Addiction Treatment Act of 2000 [11, 12]. Second, pharmacological and psychosocial treatments are not mutually exclusive and may be synergistic. Psychosocial approaches often serve as adjuncts to medications, helping to initiate and sustain recovery by eliciting lifestyle changes to build recovery capital (social, physical, personal, and cultural resources [15]) and improve overall functioning and quality of life. Third, psychosocial approaches have been shown to enhance medication adherence for health conditions that may co-occur with OUD, such as HIV [16]. Accordingly, evidence-based approaches to increase medication adherence for such comorbidities may also improve engagement with medications for the treatment of OUD, specifically. Fourth, only 35% of OUD treatment admissions incorporate the use of agonist medications in the treatment plan [1]. In parallel, less than half of US adults who resolved an opioid problem have a favorable attitude toward opioid agonist treatments, and just 60% have a favorable attitude toward opioid antagonists [17]. The causes and underlying factors of these medication attitudes are complex and largely outside the scope of this chapter. Needless to say, however, they are the subject of much discourse and ongoing research [18].

Thus, in mapping out treatment and recovery options for individuals with OUD, a comprehensive set of considerations necessarily includes psychosocial approaches. Consistent with the Institute of Medicine [19], in this chapter, we define a "psychosocial approach" as an intervention or service that leverages psychological and/or social mechanisms to facilitate health behavior change. Some also refer to psychosocial approaches as "behavioral treatments."

The current chapter is divided into four main subsections as they pertain to OUD:

1. *Psychosocial Approaches to Opioid Use Disorder: Overview and Evidence* describes each of the most common psychosocial interventions used in OUD treatment, namely, cognitive-behavioral approaches, 12-step-based approaches, brief and motivational interventions, "medication management," and contingency management, and a review of the scientific consensus regarding their effectiveness (or lack thereof).
2. *Setting an Agenda: What Do We Need to Know?* discusses important unanswered questions about psychosocial approaches to OUD that clinical research can help to answer.
3. *Clinical Recommendations* offers empirically-based clinical recommendations related to the scientific evidence that consider individual patient factors.
4. *Special Issues* discusses considerations that should be taken into account when delivering OUD psychosocial interventions, including clinical severity, life stage course, and co-occurrence of opioid use in the treatment of other SUDs.

It is important to mention that psychosocial approaches for OUD are delivered in a range of clinical- and community-based settings. Services along the entirety of the public health continuum may include psychosocial approaches: from *screening and early intervention*, before someone has developed clinically significant OUD

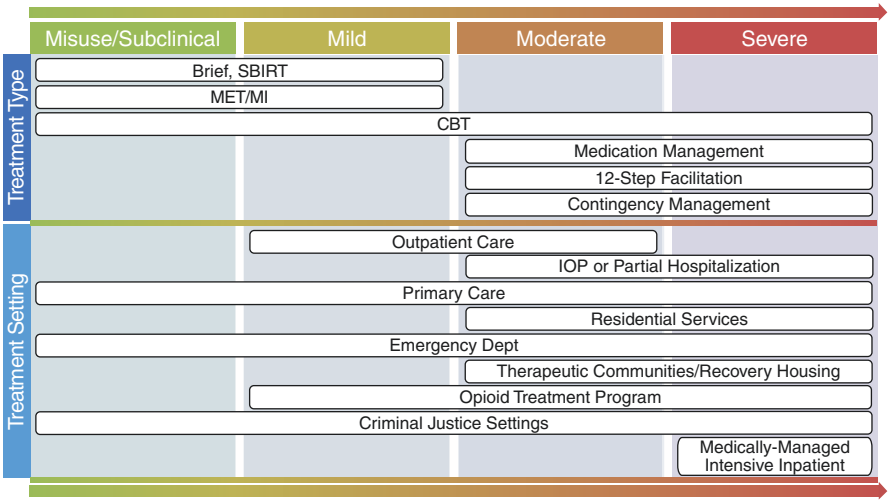

Fig. 6.1 Psychosocial approach types and delivery settings for OUD, according to the level of severity for which they are most appropriate clinically. For example, with respect to treatment type, CBT can be adapted for anyone across the full public health continuum, but brief interventions may be more clinically appropriate for individuals exhibiting subclinical misuse of opioids or mild OUD. With respect to treatment setting, individuals across the continuum may benefit from psychosocial interventions delivered in primary care, but more intensive, medically managed intensive inpatient programs are appropriate for only the most severe OUD

(i.e., primary prevention), to *active treatment*, during early stages of the disorder, facilitating OUD remission (i.e., secondary prevention), to *long-term recovery management*, intended to help individuals sustain remission over time (i.e., tertiary prevention). A brief review of settings in which treatments for OUD are provided along this continuum, also illustrated in Fig. 6.1, helps to contextualize the review of psychosocial approaches to follow.

Settings Where Psychosocial OUD Approaches May Be Delivered

1. Individuals with acute medical problems related to opioid use may be seen in the emergency department. Opioid overdoses, for example, comprise just one such opioid-related harm for which individuals present to emergency departments for care. Individuals experiencing opioid withdrawal may also engage with the emergency department to seek relief from withdrawal symptoms (e.g., gastrointestinal dysfunction and discomfort) or as a bridge to a detoxification program. Emergency departments may be a setting through which individuals can be linked to ongoing specialty treatment, in part because it is an opportunity to "strike while the iron is hot," as individuals may be more open to addressing their OUD in a time of opioid-related crisis [20].

2. Primary care offices are settings in which the largest number of individuals with OUD may be engaged, given their key roles as healthcare "gatekeepers" for many. Primary care providers can help screen for opioid problems and make referrals to specialty treatment. Importantly, primary care settings may be integral in addressing OUD through the provision of office-based buprenorphine treatment and can serve as the hub for an individual's long-term treatment engagement [7].
3. More than half of individuals receiving specialty OUD treatment—that is, at a program that caters specifically to individuals with OUD and other SUD—do so on an outpatient basis [1]. Of note, intensive outpatient programs (IOPs) provide individuals with group and individual therapy and may provide other healthcare services, like medication management, multiple times per week. These more intensive specialty treatment programs may be called "partial hospital programs" (PHPs) and are often differentiated from IOPs by more frequent treatment over a shorter period (e.g., daily for 2 weeks). PHPs also include medical monitoring of vital signs and other medical indicators of stabilization.
4. Adjunctive psychosocial approaches have traditionally been part of many methadone and buprenorphine maintenance programs. SAMHSA guidelines suggest that patients treated with medications for OUD can benefit from individualized psychosocial supports [21]. Randomized controlled trials (RCTs) that rigorously test the benefit of adjunctive psychosocial interventions, however, tell a more complex story, as outlined below in the *Psychosocial Approaches to Opioid Use Disorder: Overview and Evidence*.
5. Many residential treatment programs, where individuals live in a structured recovery-supportive environment and carry out daily activities, offer only psychosocial treatments for OUD. There exists a documented history of suspiciousness toward medications among individuals in SUD recovery, who comprise 45% of SUD providers [22, 23]. Individuals developed this suspicious attitude, in part, as a response to lived experience (including observation) with taking medication prescribed to treat their substance use and other mental health problems that ultimately led to misuse, addiction to the prescribed medications, or SUD relapse (e.g., antianxiety medications prescribed to treat alcohol use disorder) [24]. Many individuals in the SUD treatment field generalized this experience to all medicines, leading to the stigmatization of those taking OUD medications, particularly opioid agonists such as buprenorphine/naloxone and methadone. Several events, however, have led to greater openness toward the integration of OUD medications into standard clinical care. These include the accumulation of scientific evidence for OUD medications in reducing opioid use and overdose; the inclusion of medications as one of many, non-mutually exclusive SUD recovery pathways outlined by an expert consensus panel [25]; and advocacy by individuals publicly sharing their "success stories" on agonist treatment [24]. Consequently, some of the best known and highest quality residential treatment programs are beginning to prescribe and administer medications in OUD treatment [26]. Despite this increased openness toward OUD medications, psychosocial approaches are still considered frontline interventions among many residential treatment staff members, and it will likely take

time for the entire residential treatment system to embrace pharmacotherapy, particularly agonists such as methadone or buprenorphine [1].

6. Nonprofessional approaches may also mobilize and maintain recovery-supportive psychological and social changes. In addition to completely nonprofessional mutual-help groups (see Chap. 7), individuals with OUD may derive benefit from ostensibly psychosocial mechanisms of behavior change through long-term recovery residences (e.g., Oxford Houses; [27, 28]). Healthcare facilities across the United States are integrating peer recovery-support specialists on their care teams, also known as recovery coaches, who are individuals with lived OUD or other SUD recovery experience that have received specialized training to guide individuals through challenges associated with OUD. Recovery coaching may be provided in conjunction with, or as an alternative to, specialized, professional addiction treatment [29, 30].
7. About half of state and federal prisons offer psychosocial SUD treatment [31]. More than half of state and federal prisoners meet criteria for a drug use disorder and 10% use opioids weekly or more frequently [31, 32]. Only 20% of inmates with SUD, however, receive treatment [32], and few correctional facilities offer medications for OUD [33]. Although the need for access to medication treatment for OUD in correctional facilities has been receiving more attention, including through the threat of legal action by the Department of Justice [34, 35], most detainees and prisoners are not currently offered pharmacotherapy [36–38]. The American Psychiatric Association has called for jails and prisons to provide access to, and encourage participation in, nonpharmacological interventions for SUD, including individual and group counseling/psychotherapy, mutual-help groups, relapse prevention, and pre-release planning to ensure continued engagement in residential or outpatient treatment after release [39]. As more attention is paid to substantial, unmet treatment needs among incarcerated individuals with OUD (e.g., [40]), there will be greater opportunities for clinicians to provide psychosocial services in criminal justice settings, both as a stand-alone intervention and as an adjunct to OUD medication.

Psychosocial Approaches to Opioid Use Disorder: Overview and Evidence

In this section, we outline and review evidence for five classes of psychosocial approaches used to treat individuals with OUD: (1) *cognitive-behavioral approaches*, including technology-based interventions grounded in this theoretical perspective; (2) *12-step-based approaches*, including 12-step facilitation and nonprofessional, often 12-step based, services, such as recovery residences; (3) *brief interventions such as motivational interviewing* and its systems-level affiliate approach screening, brief intervention, and referral to treatment (SBIRT); (4) *medication management*, typically included as part of receiving medication for OUD in clinical trials; and (5) *contingency management*.

Cognitive-Behavioral Approaches

Cognitive-behavioral approaches comprise a suite of therapies for SUD based on cognitive therapy [41], behavioral therapy [42], and relapse prevention [43, 44]. These interventions are grounded in the premise that feelings and associated behaviors (e.g., substance use) stem from underlying thoughts and core beliefs about oneself and one's reaction to the environment. Cognitive-behavioral therapies (CBT) facilitate an individual's understanding of conditioned cues or "triggers" that go along with or precede substance use. This allows someone to develop strategies that aid in coping with potentially risky people, places, objects, or situations that can trigger thoughts, feelings, and substance use behavior. Thus, active coping with these potential triggers, including development of skills to manage them (e.g., communication, challenging one's negative thoughts, mindfulness, etc.) or avoid them entirely if possible (e.g., modifying one's social network to avoid people with whom an individual formerly used substances), features strongly in such approaches. Similarly, cognitive-behavioral approaches also might help an individual explore the role or function that substance use has played or is playing in an individual's life. With this new understanding of their substance use, individuals learn how to identify, implement, and evaluate alternative behaviors that help them to cope with distress or to find pleasure other than that which relates to substance use.

Some cognitive-behavioral approaches place greater emphasis on modifying maladaptive thinking habits and patterns, while others place greater emphasis on activities that can help modify these thinking patterns indirectly. Typically, though, they use some combination of the two. Marlatt's relapse prevention approach [43, 44] is the most popular and commonly used cognitive-behavioral approach for SUD. Relapse prevention targets an individual's abstinence self-efficacy in the face of challenging situations—i.e., perceived confidence and sense of one's abilities to stay abstinent—via strengthening of coping skills. There are many related approaches with different names, but that are very much grounded in this formative intervention. For example, mindfulness-based relapse prevention [45, 46] operates on similar treatment principles while emphasizing mindful experience of distressing feelings, particularly related to substance use cravings, and developing a meditation practice, as the primary skills through which individuals should enhance their abstinence self-efficacy. In particular, this set of mindfulness skills may help reduce impulsivity, which is a predictor of substance use relapse [47]. The community reinforcement approach [48], and its adaptation for adolescents [49], places greater emphasis on behaviors. That is, a great deal of time and effort in this intervention is dedicated to leveraging community and social supports to engage in rewarding activities that can ostensibly replace, or at a minimum compete with, the rewards derived from substance use. Newer cognitive-behavioral approaches employ similar principles, such as modifying an individual's perspective on the thoughts and feelings associated with a problem behavior, but within a novel framework. Acceptance and commitment therapy (ACT; pronounced as the word "act"), for example, uses a series of exercises to *reduce the importance* people place on their negative thoughts and instead focus on personal values to help drive behavior change [50, 51].

Technology-based interventions typically translate cognitive-behavioral approaches into digital platforms, which can increase a treatment's portability while maintaining its fidelity to the intervention as it was intended to be delivered [52]. For example, the Therapeutic Education System (TES; [53]), also licensed and branded as the FDA-approved smartphone app "ReSET" [54], is a digitized, web-based version of the community reinforcement approach. Perhaps their most unique feature, relative to face-to-face treatments, is that technology-based interventions can be tweaked and adapted to meet the needs of a variety of critical populations. TES, for example, has been adapted for, and tested in, methadone maintenance and traditional SUD outpatient programs for adults, as well as HIV prevention among adolescents in SUD treatment [55–57].

Evidence for Cognitive-Behavioral Approaches in the Treatment of OUD

Cognitive-behavioral approaches developed as part of an empirical tradition in SUD treatment and are often well vetted scientifically. As a stand-alone therapy for OUD—without the explicit aid of medication—cognitive-behavioral approaches may result in only a small benefit. While Dutra [58] found a medium effect for cognitive-behavioral approaches in the treatment of OUD, the largest benefit in this series of studies was associated with contingency management, which they regarded as a cognitive-behavioral treatment. In the current chapter, however, we delineate contingency management as a separate psychosocial approach and describe it in its own subsection to follow. Moreover, all but one study included in their meta-analysis examined the cognitive-behavioral approach as an adjunct to medication treatment. The meta-analysis, therefore, cannot speak to the effects of cognitive-behavioral approaches as stand-alone treatments for OUD. Furthermore, for individuals receiving OUD medications, RCTs have not shown a clear benefit for the addition of CBT to medication and medication management, a psychosocial intervention in its own right described below (see [59, 60], but see [61] for an exception). The TES, on the other hand, has been found to be an effective replacement for psychosocial services in methadone maintenance [55] and standard outpatient treatment among individuals with OUD [56]. Adolescents and young adults (11–21 years) with either OUD or weekly opioid use in the 90 days prior to intake (who may have also had marijuana or alcohol use disorder) receiving the adolescent-community reinforcement approach (A-CRA) in outpatient community programs responded as well to treatment compared to those with only a marijuana and/or alcohol use disorder (but no OUD or non-weekly opioid use) [49]. Despite entering outpatient A-CRA treatment with greater clinical severity, the OUD group had similar rates of treatment attendance and satisfaction compared to the non-OUD group. Both groups also evidenced similar alcohol and marijuana use at the 12-month follow-up, though the OUD group had greater use of drugs apart from alcohol, marijuana, and opioids (e.g., stimulants) and more emotional problems at the 12-month follow-up. As such, A-CRA—an empirically supported treatment for youth with cannabis use disorder [62]—may engage youth with OUD as well as non-OUD youth. The greater clinical severity of youth with OUD, however,

highlights a potential need to test more comprehensive services for these youth, including medications (e.g., [63]).

Twelve-Step Approaches

Twelve-step-based treatments are, as the name implies, interventions that leverage the philosophy, meetings, and social network of community-based 12-step mutual-help organizations (MHOs), like Narcotics Anonymous (NA) and Alcoholics Anonymous (AA), to promote health behavior change. When a treatment uses 12-step philosophy (e.g., addiction is a lifelong "disease" that requires abstinence from all substances to initiate and sustain recovery and well-being) and refers individuals to meetings in an unstructured/non-manualized way, it is often referred to as a 12-step-based or 12-step-oriented treatment (e.g., [64]). When structured, time-limited, and codified in a treatment manual, this more systematic intervention is a 12-step *facilitation* (TSF) approach [65, 66].

Many recovery residences (also referred to as "sober living" or "sober houses"), as well as therapeutic communities, are based on principles that developed in 12-step MHOs. They encourage, or more often mandate, that individuals maintain abstinence and link residents to 12-step MHO meetings in the community. The nature and quality of the services provided at recovery residences are highly variable. Organizations, such as the National Association for Recovery Residences (NARR), have developed best practice standards and have begun working with related state organizations (e.g., Massachusetts Association of Sober Housing (MASH)) to ensure that residents receive high-quality care. Regulations do not yet exist, however, that mandate recovery residences adhere to such standards. Also, of note, some recovery residences may prohibit individuals who take prescribed opioid agonists, like buprenorphine, from living there. As a function of the largely unregulated recovery residence industry, decisions are left up to each individual residence, based on the staff that started the residence, and/or the individuals who help manage it. In the case of Oxford Houses, which are guided by a set of organizational standards, the residents decide as a group who may join them as a resident. While residents may accept individuals taking prescribed buprenorphine, they may also accept them on the condition that they taper off their medication or decide not to accept individuals on agonist treatment at all [67].

Evidence for Twelve-Step Facilitation in the Treatment of OUD

TSF has much empirical support in the treatment of SUDs other than OUD, especially for alcohol use disorder (AUD) [68–72], but also for cannabis [73], cocaine [74], and other stimulant use disorders [75]. The benefits of these approaches are explained largely by TSF's ability to proactively catalyze participation in 12-step MHOs (e.g., [71, 72]). Whether TSF approaches can successfully address OUD, however, is largely unknown from a systematic, empirical standpoint. Preliminary data, however, have shown that NA attendance may enhance opioid outcomes for individuals who are prescribed buprenorphine [76] and methadone [77].

More formal evaluations of TSF for OUD are needed. One important issue for consideration is the traditional resistance to individuals taking OUD medication, opioid agonists in particular, within formal NA literature [78]. Such individuals may be viewed differently (i.e., not "in recovery") and, as a result, feel more of a muted connection to other NA members not taking agonist therapies. In a related sense, individuals taking agonist medications may experience stigma in NA, representing a potentially critical barrier to participation. In the study of NA attendance among individuals prescribed buprenorphine, for example, 25% of those who disclosed they were taking buprenorphine reported an NA member encouraged them to stop or decrease buprenorphine [76]. Qualitative data suggested those who experienced negative attitudes were less likely to go back to future meetings and more likely to consider premature cessation of buprenorphine [76]. This difficulty connecting with other NA members would ostensibly reduce the potency of 12-step MHO involvement, given its reliance on social mechanisms of recovery-related behavior change [79, 80], and could introduce potential iatrogenic effects if leading to buprenorphine discontinuation. Thus, individuals taking OUD medication may warrant special attention in future TSF clinical-scientific work.

The evidence base for recovery residences more broadly is unclear, though Oxford Houses, in particular, have good empirical support. Jason and colleagues [27, 81, 82] have found that, compared to individuals randomized to continuing care as usual after residential treatment, those randomized to live in Oxford Houses, on average, were twice as likely to be abstinent and had a $29,000 financial benefit over a 2-year follow-up window (i.e., income balanced against costs associated with incarceration and substance use) [27, 28, 82]. While the proportion of individuals in this study who had an OUD is not known, the findings suggest that Oxford Houses and other recovery residences that provide similar structure, encourage and support employment, and link individuals to 12-step MHOs all within a democratic peer-led residence, may enhance outcomes for individuals with OUD.

Brief/Motivational Interventions

Given the pervasive nature of alcohol and other drug problems among individuals interacting with the healthcare system and the ambivalence about change that characterize many with SUD [83], approaches that efficiently assess an individual's substance use problem, use strategic listening and feedback to enhance motivation, and provide brief advice play a central role in addressing OUD from a public health perspective. With durations ranging from as brief as a single, 15-minute encounter to four or more 1-hour sessions, brief interventions (BIs) are often intended to evoke a commitment to change and engage individuals in the SUD treatment system. While clinicians in specialty SUD settings may use the manualized version of this motivational interviewing (MI) style, motivational enhancement therapy (MET) [84], its appeal also lies in its versatility, as abbreviated versions can be implemented in primary care, emergency rooms, and other healthcare settings in which individuals with OUD who are not otherwise engaged in services may present for

healthcare needs. BIs provide a means to identify and effectively intervene with maladaptive behaviors in order to prevent potentially greater adverse outcomes which may result from opioid misuse or OUD. This approach is particularly useful for early intervention in emergency departments, as individuals with OUD regularly access emergency care for overdose. These emergency department visits provide an opportunity for physicians and patients to engage in thoughtful discussion about OUD and the benefits of treatment, which can ultimately motivate patients to take important steps toward behavioral change and recovery. When the explicit goal of this approach is treatment engagement, if clinically appropriate, the intervention is called screening, brief intervention, and referral to treatment (SBIRT). Brief interventions are modeled on a series of elements known by the acronym FRAMES, which entail F) providing *f*eedback about risk, R) tasking an individual with the *r*esponsibility for change, and A) providing the individual with *a*dvice as well as M) a *m*enu of treatment and recovery strategies, all within E) an *e*mpathic counseling style that S) aims to evoke an individual's *s*elf-efficacy to make change [85, 86]. Such an early intervention or prevention approach is thought to alter an individual's health behavior trajectory so that they avoid substantial substance-related harms.

Evidence for Brief/Motivational Interventions in the Treatment of OUD

In the context of methadone maintenance programs, as few as three sessions of MI may improve overall drug use outcomes, relative to non-MI health promotion sessions [87], and may enhance treatment expectations and improve opioid outcomes [88]. In general hospital settings, MI helped reduce prescription drug use in nontreatment-seeking individuals with problematic prescription drug use (primarily opioid use; [89]) at the 3-month follow-up, though effects decay by 12 months [90]. A single MI session delivered to individuals with problem opioid use in an emergency department setting may reduce the risk of opioid overdose as well as levels of opioid misuse 6-months post-intervention [91]. In primary care settings, a single MI session has also been shown to decrease opioid use problems in individuals at moderate risk for OUD [92]. Although studies suggest MI is often superior to no treatment comparison conditions, systematic literature reviews suggest its benefits do not exceed treatment as usual (TAU) for SUD overall [93, 94].

Regarding SBIRT, there is a general dearth of studies specific to individuals with OUD. That said, among individuals using opioids only or a combination of opioids and cocaine in a general medical clinic, those who received MI, active referral, and a written list of treatment referral resources followed by a 10-day follow-up phone call had fewer drug-positive hair toxicology screens 6-months post-intervention than control group participants who received only a written list of treatment referral sources [95]. On the other hand, in primary care patients with weekly or greater drug use (or a drug use consequence), one-fifth of whom identified opioids as their primary substance, MI interventions yielded similar drug use outcomes to no added intervention 6 months later, regardless of the primary substance. While unclear precisely why SBIRT is typically effective in reducing drinking, but not use of other drugs such as opioids, one explanation may be that drinking

is viewed as part of a series of lifestyle choices (e.g., diet, exercise, alcohol intake) responsive to SBIRT. Other drug use, however, is illegal, and individuals using other drugs despite this risk may experience reward to a degree so great that their use is resistant to the BIs provided in SBIRT [96]. Greater evidence for this hypothesis is that drinking-related benefits for SBIRT are less clear among those with heavy drinking or moderate to severe AUD [97]. While potent BIs to address opioid misuse have not yet been developed [98], screening in medical settings is an important first step toward helping individuals with drug use problems find the appropriate avenues for treatment [99].

"Medication Management"

RCTs testing medications for OUD, such as buprenorphine/naloxone, often include, as part of the medical intervention, a psychosocial clinical component, consisting of ongoing medication monitoring, weekly or more frequent check-ins, and advice [59, 60, 63, 100, 101]. This psychosocial approach is typically referred to as "medication management" (MM). The precise nature of this approach is conditional on the study in which it is tested, though such approaches overlap in several noteworthy ways. They are provided on a regular basis, often weekly or multiple times per week at first, with tapering of frequency over the duration of the medication trial. MM is usually semi-structured and outlined in a manual, though perhaps explicitly codified to a somewhat lesser degree and less reliant on any specific theoretical orientation than other psychosocial approaches. A healthcare professional, such as a physician or more often a nurse practitioner or other nursing professional, assesses the individual's functioning since the last visit, including their adherence to medication, and overall SUD-related change experience. Such assessments might include any challenges faced and brief, directive counseling on how to cope with such challenges going forward. MM often employs referral to 12-step and other MHO groups in the community as well. These approaches are not typically considered "psychosocial interventions" in the traditional sense, given their role as part of the medical intervention delivered with the medication under study. However, MM is nonetheless a psychosocial intervention as defined in this chapter and by the Institute of Medicine [19], as it mobilizes social, cognitive, and behavioral mechanisms to enhance health and well-being. The degree OUD prescribers implement MM in clinical practice, in ways analogous to its implementation in actual clinical trials, is not known. As is the case for most psychosocial interventions, there is likely to be some degree of deviation from MM as delivered in RCTs compared to "real-world" practice, given the rigorous oversight and monitoring in clinical trials. Such an assumption, however, must be tested empirically.

Evidence for Medication Management in the Treatment of OUD

The independent therapeutic benefits attributable to MM alone are not known empirically. This intervention is viewed as part of a comprehensive medical intervention, rather than an adjunct. Given that some clinical programs mandate

psychosocial treatment in order to receive agonist medication, there have been several calls for a "medication-first" approach, where a psychosocial intervention would not be required and may be viewed as ancillary or even unnecessary (e.g., [102]). Among individuals receiving methadone, for example, a medication-only approach (provided on an interim basis) produced similar heroin and cocaine outcomes to a more comprehensive approach including required counseling [103]. The study results are confounded, however, by type of methadone administration where the medication-only group needed to attend the clinic in order to receive methadone, while the group who received comprehensive services was able to get take-home doses. The additional accountability provided by requirements to attend the clinic may have helped boost effects of this "medication-only" condition.

Overall, based on available evidence, it is unclear whether an OUD medication's effects on reduced opioid use and other important public health outcomes remain as potent in the absence of the therapeutic contact, accountability, and oversight and monitoring, that MM can provide, warranting future investigation. Such investigations would help determine whether simple prescription, with very brief or no monitoring or clinician check-ins, produces similar opioid and treatment retention outcomes as prescription with more robust MM. If such MM check-ups and counseling are not found to add any therapeutic benefit, then prescribing policies could be changed, ultimately saving time and money.

Contingency Management

Operant conditioning theory [104–106] posits that humans are likely to repeat behaviors that are rewarded (e.g., leading to a pleasurable feeling) and decrease behaviors that are punished (i.e., leading to an unpleasant feeling). This theory also suggests that the immediacy of this behavioral response—how close in time the reward or punishment follows the behavior—can play a powerful role in shaping such behavior [107]. SUD researchers capitalized on these well-known psychological phenomena to develop contingency management (CM). Treatment adherence (e.g., attendance) and substance use are the two most commonly targeted outcomes in this regard. CM can be implemented in a variety of ways, though voucher-based reinforcement is the most commonly studied approach. In this paradigm, patients receive a voucher with a monetary value that can be exchanged for actual money or a prize if, on testing, their urine toxicology screen is negative, indicating that they have been abstinent from the target substance(s) (e.g., illicit opioids). CM paradigms are often also characterized by increasing escalation of the amount of reward, with each additional consecutive negative toxicology screen [106] resulting in greater value rewards to incentivize individuals even further to continue to maintain abstinence over longer periods of time.

Evidence for Contingency Management in the Treatment of OUD

Based on scientific evidence, CM is widely regarded as the most potent psychosocial intervention for SUDs such as cocaine use disorder [58, 106, 108]. While CM targeting specific drug classes during outpatient opioid agonist treatment, such as

methadone maintenance, may reduce the non-medical use of cocaine, tobacco, and polysubstance use (e.g., cocaine plus opioids), its effects over and above opioid agonist treatment might be less pronounced when CM targets opioid use alone, is administered for fewer than 12 weeks, or is used alongside opioid agonist treatments other than methadone [109, 110]. That said, CM administered among outpatients with OUD, with or without naltrexone, has been shown to improve treatment retention (difference of 1.8 weeks) and increase opioid abstinence (difference of 5 more opioid-free urine specimens) relative to naltrexone alone [111]. In addition, opioid-targeted CM administered alongside CBT (i.e., community reinforcement approach) in the context of buprenorphine taper during detoxification has been shown to improve opioid abstinence duration and treatment completion relative to lifestyle counseling [112]. Importantly, CM is likely to produce similar outcomes irrespective of incentive value or type (monetary vs. other) [109, 113].

When CM is used to guide agonist treatment, it may also yield recovery benefits. Providing take-home doses of methadone for OUD treatment, contingent upon weekly drug-free urine specimens and clinical stability, is shown to decrease the risk of treatment dropout relative to standard supervised methadone administration. Furthermore, individuals provided a take-home methadone regimen without contingencies may be less likely to show improvement in psychiatric functioning, relative to those receiving contingency-based take-home doses (e.g., contingent on providing negative urine toxicology screens) or standard supervised methadone treatment [87]. In addition, rewarding methadone patients for attending scheduled psychiatric sessions as part of treatment facilities' on-site integrated care programs can increase session attendance and adherence to psychiatric medications during the early stages of treatment (1–3 months), but may fail to yield benefits over standard on-site integrated care with regard to substance use outcomes [87].

As noted previously, fewer investigations have assessed psychosocial treatments as adjuncts to buprenorphine or naltrexone treatment compared to methadone, yielding mixed findings. Controlled investigation of CM administered with or without CBT suggests that buprenorphine treatment may not significantly benefit from psychosocial adjuncts. During buprenorphine treatment, CM (escalating incentives for weekly drug-free urine) and CBT, whether administered alone or in combination, have yielded equivalent outcomes to TAU (e.g., medication management only). Objective measures of treatment retention and compliance, psychosocial problem severity, withdrawal, and craving are generally unaffected by these psychosocial treatment adjuncts, despite patients' own subjective perceptions of their increased effectiveness during buprenorphine treatment [87]. Conversely, other investigations of CM for buprenorphine patients have demonstrated CM's ability to produce longer durations of opioid and other drug (cocaine) abstinence and more drug-free (opioid and other drug) urine specimens than buprenorphine TAU (e.g., standard counseling [114]). Regarding naltrexone, the use of CM to motivate opioid antagonist treatment receipt and adherence has been assessed via controlled investigation in the context of a therapeutic workplace (workplace participation contingent upon naltrexone treatment). Results showed oral naltrexone patients who also received CM had increased rates of oral and injectable naltrexone compliance and treatment completion, greater

injectable naltrexone retention, and more opioid-negative urine samples than those who did not receive CM [87].

Nonetheless, the current state of the science is limited, as only a handful of CM studies have incorporated follow-up post-intervention, producing few studies suitable for large-scale meta-analysis of CM specifically to address OUD [109]. Thus more work is needed to evaluate the effects of CM on opioid-specific outcomes since many studies conducted to date assess cocaine outcomes in opioid- and cocaine-dependent patients taking agonist medications like methadone. Further investigation is also needed to assess benefits of CM for OUD patients who are not taking OUD medication. Finally, additional research is required to identify potential moderators of CM outcomes, including age, gender, race/ethnicity, treatment setting, and co-occurring medical and psychiatric disorders, to help determine the extent to which certain subgroups are more or less responsive to CM.

Setting an Agenda: What Do We Need to Know?

As shown in Table 6.1, several unanswered empirical questions remain to be addressed before definitive recommendations on psychosocial approaches for OUD can be offered. The most pressing need appears to be what psychosocial approaches provide benefit over and above the effects of medications and medication management. Given that structured CBT, shown to be helpful for other SUD, seems to add little to OUD medication interventions—including medication management visits—alternative approaches should be examined. TSF approaches are promising candidates given their effectiveness in the treatment of other drug use disorders and their ability to link individuals with community-based 12-step MHOs, participation in which may be associated with improved opioid outcomes among those taking buprenorphine [76]. In light of the traditional rift between 12-step MHO sources and medications for OUD, psychosocial approaches that target individuals' social networks in a broader way, like Litt's Network Support [71, 115]—where 12-step MHOs are but one way to modify an individual's social network—may be considered. Furthermore, dismantling studies that test medication alone compared to medication with medication management and other forms of professional support can help determine the unique effects of this psychosocial approach virtually always paired with medication in clinical trials. If, for example, medication alone does as well as medication with additional management, resources can be devoted more systematically to engaging individuals with medication while de-emphasizing the use of psychosocial support. Motivational interventions specifically designed to enhance OUD medication adherence [116] may be included and tested in these dismantling interventions.

A series of studies on recovery management checkups showed that long-term monitoring, including quarterly check-ins with linkage to treatment re-engagement, when needed, for individuals with SUD, is an effective and cost-effective strategy to improve outcomes and lower costs [117, 118]. Only one-fifth of participants were opioid-primary, and, as such, this recovery management approach

Table 6.1 Psychosocial approaches for OUD. Descriptions, delivery settings, strength of evidence in addressing OUD, and recommendations

Approach	Description (typical delivery/# of sessions)	Settings delivered	Strength of evidence	Recommendations
Cognitive-behavioral therapies (CBT)	An array of approaches based on learning principle: teaches the patient to identify and modify thinking and behavior regarding their substance use and related consequences (Manualized interventions typically designed for 12–18 weekly individual sessions, though can also be delivered as part of group therapy)	Outpatient, primary/clinical care settings, telehealth	Weak (alone), moderate in combination with medications	Deliver with medications whenever possible; for adolescents and young adults with OUD, the adolescent-community reinforcement approach should be a first-line psychosocial intervention given its demonstrated acceptability in this group of patients
Twelve-step facilitation (TSF)	Emphasizing addiction as a chronic medical disease, TSF systematically links patients to, and encourages active engagement in, community-based 12-step MHOs, like NA, to promote health behavior change (Manualized interventions typically designed for 4–12 weekly individual sessions, though can also be delivered as part of group therapy)	Outpatient, primary/clinical care settings, residential treatment programs, long-term recovery residences	Insufficient	For patients receiving OUD medication, in particular agonists, clinicians should prepare them for stigma they may encounter in 12-step MHOs and help them find meetings that support individuals taking OUD medications
Motivational interviewing (MI), brief intervention (BI), SBIRT	Time-limited and goal-oriented intervention to help the individual understand that their substance use is putting them at risk and help the patient tap into his/her motivations to reduce substance use and engage in treatment (Brief, single sessions of 15 minutes to four sessions of more in-depth therapy)	May be delivered opportunistically by a range of trained addiction specialists or nonspecialists in various settings: primary/clinical care settings, emergency departments, general hospital	Moderate (in comparison with no/minimal treatment)	Suitable as an early intervention for patients exhibiting problematic or risky substance use, which has not yet progressed to more severe OUD

Medication management (MM)	Semi-structured assessments delivered regularly as part of a comprehensive medical intervention; ongoing monitoring of medication adherence and substance use combined with brief counseling, psychoeducation, and referrals to MHOs (Visits while providing medication, often weekly or twice weekly, with gradual tapering in frequency over time)	Delivered by a medical professional (physician, nursing professional) as part of outpatient OUD pharmacotherapy	Insufficient, cannot disaggregate from medication effects	Recommended at the initiation of OUD pharmacotherapy; can be delivered either alone, for less complicated patients, or in conjunction with another psychosocial intervention for patients with higher severity OUD and more complex psychosocial needs
Contingency management (CM)	Behavioral approach based on principles of operant learning theory; employs positive reinforcement via therapeutically-applied incentives (i.e., vouchers, "lottery" prizes) to incentivize treatment adherence and/or reduced opioid use demonstrated through objective evidence such as negative toxicology results (Interventions typically for 12 weeks or more, with urine toxicology screens and affiliated rewards typically conducted multiple times per week)	Outpatient, primary/clinical care settings (limited by the high cost of implementation), criminal justice (i.e., drug courts, probation supervision)	Strong for treatment adherence and non-opioid drug use; insufficient for opioid use specifically	Recommended as an adjunctive strategy to enhance adherence and non-opioid drug use in methadone maintenance; unlikely to hurt as an adjunct to buprenorphine, though it may not help over and above MM; for individuals who refuse medications, CM should be delivered if adequate resources are available

warrants in-depth investigation among individuals with OUD, specifically, both for those taking OUD medication (e.g., [119]) and those who choose a non-medication recovery pathway.

There will always be a subset of individuals with OUD who choose a non-medication pathway to resolve their problem. While the precise number of individuals with negative medication attitudes remains unknown, and motivational strategies may be designed and tested to engage individuals with pharmacotherapy, strategies are needed to help medication-resistant individuals to initiate and sustain OUD remission. It is likely that for those with severe OUD who choose a non-medication pathway, structured services that provide psychosocial scaffolding give them the best chance of success. Therapeutic communities, long-term residential treatment, and recovery residences may help address this need. Research on the effectiveness of such options for individuals who do not want to take OUD medications, and the cost-effectiveness of these options, will help determine clinical and public health recommendations.

SBIRT has been largely ineffective for individuals with non-alcohol SUD [99]. Strategies that are more intensive and innovative could help to better engage individuals with OUD in treatment. For example, Scott and colleagues piloted an intervention that leverages the knowledge and experience of peer workers (those who are in OUD recovery themselves) to engage individuals in methadone maintenance treatment [119]. In addition, technology-assisted approaches may be particularly helpful in engaging individuals with less severe OUD profiles in treatment. These individuals may not want or need to modify their lives in substantial ways to seek treatment. While some of these approaches are only available in professional contexts, via a physician's prescription, for example, others are free and widely available, including existing online recovery support groups [120, 121]. These low-threshold, easily accessible recovery options may be attractive to the 85% of individuals with current drug use disorder who do not seek services [122], as well as the additional 11 million Americans who misuse opioids but do not meet diagnostic criteria for an OUD [123].

Clinical Recommendations

The available evidence on psychosocial approaches for OUD, in combination with evidence in the treatment of other SUD as well as clinical experience, points to several recommendations. While each of the following recommended approaches may not be feasible financially or logistically, efforts made toward following these recommendations are likely to produce better substance and related outcomes for individuals with OUD.

1. Individuals taking OUD medications should receive medication management, including monitoring, feedback, and encouragement, to engage in recovery support services. For the goal of reducing opioid use, CBT may not be required over and above medication management, if medication management is delivered as faithfully and intensively as in rigorous RCTs.

- Adolescents, however, should receive empirically supported psychosocial approaches in addition to medication, given that medication benefits have only been observed, to date, in the context of robust treatment program participation [63]. A-CRA may be an appropriate intervention in this context. While not tested explicitly in combination with medication, OUD treatment-seeking adolescents and young adults attend sessions as much as their non-OUD (i.e., alcohol and marijuana use disorder) counterparts [49].

2. Individuals in methadone maintenance should receive CM to help reduce rates of other, non-opioid drug use, such as cocaine use.
3. For patients receiving buprenorphine and other agonist treatments, clinicians should preemptively discuss negative attitudes they may encounter in 12-step MHOs. While not tested empirically, recommendations to attend MHOs are part of many medication management protocols, and thus it may be helpful to problem solve barriers to engagement with patients, particularly as related to potential negative medication attitudes they may face when interacting with other 12-step MHO attendees. Referrals to non-12-step MHOs and other strategies to aid social network modification (e.g., volunteering, gym classes, etc.) may be helpful in this regard.
4. For individuals who refuse medications, intensive, wrap-around services are recommended. This suite of services should include empirically supported approaches, such as CM, as well as promising recovery housing avenues, such as Oxford Houses, which have been shown to be cost-effective among individuals with a range of SUD.
5. In the emergency department and other acute care settings, in the absence of other clinical options (e.g., engagement with buprenorphine and medication management), MI should be delivered to address potentially problematic opioid use. Effects, however, are likely to decay within months, and outreach may be needed to assess and refer patients to appropriate care as needed.
6. Long-term recovery management should be implemented with OUD patients, as outlined in recovery management checkups. This intensive monitoring protocol involves quarterly check-ins and assessments over the course of at least 2 years, MI if determined to have a need for clinical services, and active linkage to treatment.

Special Issues

There are several interrelated issues to consider as part of these recommendations when implementing psychosocial interventions for OUD. Chief among these are developmental life course stage, opioid use severity, and non-primary opioid use.

Life Course Stage

The life course perspective in substance use disorder treatment and recovery [124, 125] suggests that developmental stages of the life course may influence factors

related to both SUD onset and offset/recovery. Adolescence (12–17 years), emerging adulthood (18–29 years), established adulthood (30–59 years), and older adulthood (60+ years) may be useful developmental stages to contextualize OUD treatment and recovery. As an example of the complexities introduced when considering life stage course, among US youth with OUD, emerging adults may be more likely than adults 30 and older [126], as well as adolescents [127, 128], to receive OUD medication, such as buprenorphine/naloxone. It is worth nothing, however, that despite their greater relative engagement with OUD medications compared to other age groups, most emerging adults with OUD do not receive OUD medication [127]. In addition, among 5-year age groupings, young adults 25–29 years old constitute the largest proportion of individuals who present to treatment that identify opioid as their primary substance [1]. At the same time, emerging adults have worse buprenorphine treatment outcomes than older adults, including treatment retention and opioid-negative toxicology screens [129]. While the specific reasons for their poorer outcomes have not been examined empirically, lower initial motivation to reduce or quit opioids, less social structure coupled with still-developing frontal brain structures responsible for planning and organization, and high levels of psychological stress may account for these poorer outcomes [130]. Irrespective of what explains their clinical challenges, emerging adults may require special clinical attention to help initiate and maintain treatment engagement.

Regarding adolescents, the American Academy of Pediatrics recommends offering medications for OUD or referring to providers that can prescribe such medications [131]. The studies on which this recommendation is based (e.g., [63]) also paired medications with intensive behavioral treatments including a combination of individual and group therapies. This suggests, based on available evidence, that best practices should include a combination of medication with behavioral treatment. As might be expected, adolescents presenting to treatment with problem opioid use are often more severe clinically and have riskier social environments (e.g., a greater proportion of peers regularly using alcohol and other drugs) than their counterparts with only alcohol or marijuana problems [132, 133]. As with adults, the optimal psychosocial approaches that should be implemented with OUD medications for adolescents have not been examined scientifically. Another important consideration with adolescents is the medication views of their parents and other caregivers. Anecdotally, many parents of adolescents with OUD are concerned about potential short-term and long-term side effects of agonist medications, like buprenorphine/naloxone. Clinicians may wish to establish a collaborative treatment plan with the adolescent and parent that can address such concerns, including a comprehensive discussion of benefits and risks for the medication, disabusing them of concerns that are not consistent with available scientific knowledge, and if necessary, conceptualizing the medication regimen on a "trial basis," and offering to discuss a treatment plan that does not include OUD medication.

Comparatively less is known about older adults with OUD compared to younger age groups [134]. Existing data suggest that older adults may respond better to

treatment, including better opioid outcomes across many different types of treatment [134]. While the reasons for these better outcomes are not known, it is possible that older adults have greater recovery capital and opportunities for recovery support in their social networks [135]. More studies are needed, however, before definitive recommendations for treatment of OUD among older adults can be made.

Severity

Diagnoses of all SUD, including OUD, in the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (*DSM-5* [136]), are specified by the level of severity, based on the number of criteria presented. Two or three criteria constitute mild OUD, four or five constitute moderate OUD, and six or more symptoms indicate severe OUD. Individuals with severe OUD often receive more attention in clinical and public health research than those with mild or moderate OUD variants, given they suffer the worst consequences and are more likely to have characteristics associated with treatment seeking, including physiological symptoms and a perceived inability to control their opioid use [137]. The proportion of US adults, however, with current *mild* drug use disorder including, but not limited to, OUD matches that of the proportion with moderate and severe variants combined [122]. Furthermore, while 2.1 million Americans meet diagnostic criteria for OUD, another 11.4 million misuse opioids but *do not* meet OUD criteria (i.e., *subclinical misuse*) [123]. Given risks of life consequences associated with opioid misuse including, but not limited to, opioid overdose, these individuals with mild OUD and subclinical misuse require clinical attention as well. As mentioned above, strategies to deal with milder forms of alcohol misuse and problems, like SBIRT, have not been shown to work among individuals with other drug problems, such as opioids [99]. In fact, in clinical samples, individuals with opioid misuse, compared to those with OUD, may actually have worse opioid outcomes [138]. OUD medications primarily aid in reducing physiological manifestations of the disorder, such as craving and tolerance, and may not be appropriate for those with mild OUD or opioid misuse. At the same time, community-based resources, such as NA, may also cater to those with greater levels of OUD severity, given the robust association between 12-step MHO participation and clinical severity in treatment samples [139]. Clinicians may wish to address mild OUD and opioid misuse with psychosocial interventions such as CBT or MI/MET. At a minimum, clinicians may wish to provide patients with opioid overdose education and encourage patients to obtain naloxone (e.g., [140, 141]). Education may include, for example, knowledge regarding opioid effects, opioid overdose signs and risk factors, and overdose response [141]. Additionally, technology-based versions of these interventions [142] could be appropriate, as they may require less initial motivation and allow individuals to engage in addressing opioid use at their own pace and with unique, patient-centered goals, rather than engaging in a structured OUD treatment program.

Non-primary Opioid Use

Individuals with mild and subclinical opioid misuse may, however, have other SUD and present to treatment where another drug, such as alcohol, is the primary problem substance for which they are seeking treatment. Data from COMBINE, an AUD trial testing combinations of medication and psychosocial interventions conducted in the mid-1990s, suggest opioid misuse—in the absence of OUD—predicts poorer drinking outcomes, including a greater likelihood of alcohol relapse [143]. In addition to interventions designed to facilitate opioid abstinence, opioid overdose education and naloxone distribution, as noted above, are recommended.

Summary and Conclusions

Comprehensive public health responses to recent increases in OUD and opioid misuse-related harms require an understanding of available psychosocial approaches and their potential utility. Many empirically -supported psychosocial approaches for non-opioid SUD, including CBT, TSF, and SBIRT, have weak or insufficient evidence to support their utility for OUD and opioid misuse at present. An important, lingering empirical question is whether cognitive-behavioral approaches remain unnecessary over and above medication management even when pharmacotherapies are delivered in real-world clinical settings, which likely do not have the resources to deliver medication management with as much fidelity and structure as was done in randomized trials [114]. Other approaches, like MI, are likely to be helpful in emergency departments and general hospital settings, where individuals may demonstrate increased motivation after experiencing a severe health consequence of opioid misuse, though these effects may decay after just a few months. Clinical research has focused primarily on OUD pharmacotherapies, a necessary emphasis given the current, urgent public health need in the US, in particular, to address sharp increases in drug overdoses involving opioid use. CM, when possible, may be an effective strategy to address non-opioid drug use and enhance OUD pharmacotherapy adherence. To provide an optimal public health response to OUD, studies should investigate which psychosocial approaches, if any, can further enhance the effects of pharmacotherapy and whether medication management (tested alongside OUD medications in virtually all RCTs) is, in fact, needed to produce the best possible outcomes. Finally, given evidence that some patients may be reluctant to engage with pharmacotherapy, additional research is needed to inform clinical recommendations on the most effective psychosocial interventions and other recovery support approaches for this important but understudied cohort.

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Mutual Help and Peer Support Models for Opioid Use Disorder Recovery

7

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Abbreviation

AA	Alcoholics Anonymous
AUD	Alcohol use disorder
BMT	Buprenorphine maintenance treatment
CA	Cocaine Anonymous
CARC	Certified Addiction Recovery Coach
CASAC	Credentialed Alcoholism and Substance Abuse Counselor
CBT	Cognitive behavioral therapy
CCAR	Connecticut Community for Addiction Recovery
CMA Treatment Advocate	Certified Medication Assisted Treatment Advocate
EDs	Emergency departments
EMRs	Electronic medical records
GDC	Group drug counseling
IGC	Individual group counseling
MARS Project	Medication Assisted Recovery Services Project
MAT	Medication-assisted treatment
MHOs	Mutual-help organizations

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MMT	Methadone maintenance treatment
NA	Narcotics Anonymous
NAMA Recovery	The National Alliance for Medication-Assisted Recovery
NIDA	National Institute of Drug Abuse
OASAS	Office of Alcoholism and Substance Abuse Services
ODC	Opioid drug counseling
OUD	Opioid use disorder
RCT	Randomized controlled trial
REBT	Rational Emotive Behavioral Therapy
RR	Rational Recovery
SAMHSA	Substance Abuse and Mental Health Services Administration
SMM	Standard medical management
SOS	Secular Organization for Sobriety *or* Save Our Selves
SUD	Substance use disorder
TAU	Treatment as usual
TSF	Twelve-Step Facilitation

Introduction

The onset and offset of opioid or other drug use disorders involve the dynamic interplay of biological, psychological, and social processes. Most people are first exposed to substances via social mechanisms; friends or family introduces the formerly unexposed individual to a substance. Prior to this, typically through direct social observation and modeling, psychological factors of curiosity and substance-related positive cognitive expectancies (e.g., "drug use looks like fun") work to create the fertile ground that increases receptivity to initial offers. The potent subjective euphoria or stress relief often experienced with initial consumption of a psychoactive substance leads to the germination of these initial seeds of exposure, manifested by a strong desire to remember and repeat the experience. When fertilized by the right social context (e.g., close friends who endorse, model, and encourage the behavior), repeated exposure, neurobiological change, and the growth of an addictive process can ensue.

It is noteworthy, however, that just like the onset of opioid or other drug use, the offset is also strongly influenced by social factors. The National Institute of Drug Abuse (NIDA), for example, states that there are four main reasons why people begin to use drugs: To feel good, to feel better, to do better, or because other people are doing it [1]. We would argue that, paradoxically, these are the same four reasons why people *stop* using drugs: to feel good, to feel better, to do better, and *because other people are (not) doing it* (Table 7.1). In other words, as an individual goes through the phases of a drug use disorder from the initial pleasure, relief, and performance enhancement that a substance can initially provide, through to the subsequent pain, angst, and diminished performance that the same substance later induces, social influences that once attracted, modeled, reinforced, and facilitated drug use can equally and powerfully attract, model, reinforce, and facilitate *non*-drug use and increase the chances of remission and long-term recovery. Consequently, such social forces have been leveraged therapeutically.

Table 7.1 The paradox of substance use

Four main reasons why people *start* taking drugs	Four main reasons why people *stop* taking drugs
To feel good	To feel good
To feel better	To feel better
To do better	To do better
Because other people are doing it	Because other people are *(not)* doing it

This chapter examines the role that these social forces and growing therapeutic "peer support" models, including Recovery Coaches and mutual-help organizations (MHOs) such as Narcotics Anonymous (NA), can play in facilitating opioid use disorder remission and long-term recovery. The content is divided into three main subsections:

1. *Origin and Nature of Peer Support Recovery Models.* In this section a brief historical overview of the origin and growth of peer MHOs is provided. This includes Alcoholics Anonymous (AA) and its successor, Narcotics Anonymous, and describes the nature and growth of other secular MHOs that have emerged in more recent decades (e.g., SMART Recovery, LifeRing Secular Recovery). New models of Recovery Coaching/peer support that have emerged from the work of MHOs and its evidence base are also described.
2. In Sect. 7.2, *Research on Peer Models of Recovery*, the scientific evidence addressing the clinical, public health, and economic utility of both MHOs and Recovery Coaching models in the treatment of, and recovery from, opioid use disorder is described and appraised.
3. Finally, in Sect. 7.3, *Clinical and Policy Implications of the Science of Peer Support Models for Addressing Opioid Use Disorder*, the clinical and policy implications related to the scientific evidence regarding peer support models in addressing opioid use disorder are discussed.

Origin and Nature of Peer Support Recovery Models

Alcohol and other drug use disorders confer a prodigious burden of disease, disability, and premature mortality in middle- and high-income countries globally, leading to economic costs on most societies that often run into the hundreds of billions of dollars annually. Opioid misuse and opioid use disorders (OUDs) have substantially increased recently in the United States, as well as in other higher-income countries, resulting in epidemic levels of opioid overdose deaths [2, 3]. The deleterious impact of chronic alcohol and other drug use on the brain is also well documented and has shown to have increasingly negative impacts on its structure and function, particularly in the neurocircuits involved in reward, memory, motivation, impulse control, and judgment [1, 4–6]. Addicted individuals, therefore, struggle with an increasingly impaired ability to regulate the impulse to use substances despite negative consequences related to substance use [4, 5]. Though it is possible

for affected individuals to stop harmful substance use with treatment and support, they remain susceptible to relapse in the early months and years of remission, as it can take an additional 4–5 years after achieving sustained remission (i.e., 1 year without symptoms) for an individual's risk for meeting criteria for substance use disorder (SUD) to be no higher than that of the general population (i.e., to be at or below 15%) [7, 8]. This is due, in part, to the fact that for many affected individuals, it takes time for biopsychosocial stabilization and reparative work to occur within the brain. Moreover, re-exposure to people, places, or mood states that have become strongly associated with substance use through classical conditioning can also increase craving and the risk of substance use. Opioid and other SUDs are similar to other chronic conditions in that these disorders often require ongoing recovery monitoring and recovery management to support early and continued remission and facilitate intervention should relapse occur [9, 10].

Most societies implement a number of policy, public health, and treatment measures to address these endemic SUD problems. While professional treatment implementation efforts are considerable, the prevalence and chronic nature of these conditions and long-term susceptibility to SUD recurrence mean that professional resources alone are typically stretched to cope with the demand for long-term recovery monitoring and management strategies that can help sustain remission over the long term. Perhaps in tacit recognition of these unwelcome facts, particularly by sufferers and their families themselves, a number of indigenous, free community-based peer-led resources have emerged and grown substantially in many countries to help initiate and sustain recovery-related changes.

The oldest and most prevalent among these are mutual-help organizations, such as AA, NA, and other 12-step based entities, as well as newer entities, such as SMART Recovery, LifeRing, and Celebrate Recovery [11]. While these organizations differ in origin, scope, focus, prevalence, theoretical orientation, and behavior change and maintenance strategies, there are many therapeutic elements common to all of these ostensibly different organizations, which may confer the majority of the therapeutic benefits derived from engagement with them [12–14]. These freely available peer support recovery models of MHOs and the positive research findings from participation in them have given rise to more formalized models of peer support increasingly known as "Recovery Coaching." Below, we describe several of these ubiquitous 12-step MHOs and other newer MHOs and Recovery Coaching models that address opioid use disorders (Table 7.2).

Narcotics Anonymous

In 1898, Bayer began selling diacetylated morphine under the trade name "heroin" as a cough treatment [20]. Initially believed to be less habit-forming than morphine, diacetylated morphine was readily available in the United States [20]. But by 1910, Americans were crushing and inhaling this new compound, a problem that was particularly prevalent among young working-class men [20]. Around the same time, physicians were growing conflicted about the use of pain

Table 7.2. Mutual-help organizations for opioid use disorder

Name and Website	Target problem	Number and location of groups in the United States	Theoretical orientation	Therapeutic goal(s)	Assumptions about addiction	Key interventions
Celebrate Recovery [15] celebrate recovery.com	All addictive behaviors	~2800 groups in 50 states and D.C.	12-step	Abstinence	Addiction is a patterned response to painful experiences	Surrendering to God, the "one and only" higher power Working the "Christ-centered" 12-steps Following the Eight Recovery Principles Having an "accountability partner" and "sponsor" (i.e., mentor)
LifeRing [16, 17] lifering.org	Any drug, including alcohol	~150 groups in 15 states; online meetings	Humanistic/ existential	Abstinence	Addiction is biological and psychological	Empowering one's "sober self" and weakening one's "addict self" Developing and following an individualized Personal Recovery Program (PRP) Self-empowerment
Narcotics Anonymous [18] na.org	Any drug, including alcohol	~27,250 groups in 50 states and D.C.; online meetings	12-step	Abstinence	Addiction is a chronic disease Individuals do not have control over their addictions	Believing in and surrendering to a higher power of one's own choosing Working the 12-steps Having a "sponsor" (i.e., mentor)
SMART Recovery [19] smart recovery.org	All addictive behaviors	~2000 groups in 49 states and D.C.; online meetings	Cognitive-behavioral	Abstinence recommended, though moderate use acknowledged as a possibility	Substance use and addiction is caused by ineffective coping strategies	Increasing and maintaining motivation Managing feelings, thoughts, and actions Learning to cope with urges

medication. On the one hand, opioids were an effective way to minimize patients' pain, while on the other, addiction in patients and street use of morphine were rapidly increasing problems [20]. Though federal efforts soon followed in an attempt to control opioid production, importation, and distribution, little help was available for those addicted to opioids.

It was not until 1935 that a seemingly inconspicuous meeting in Akron, Ohio, brought together the future founders of AA that would later lead to the founding and worldwide dissemination of AA [21]. At the same time, the US Public Health Service Hospital—the first federal prison hospital that was known as a "Narcotics Farm"—opened in Lexington, Kentucky in 1935 [21, 22]. Whereas at that time alcohol was "culturally celebrated" [22] following the end of prohibition, and AA's founders and members were able to work somewhat more openly to grow the organization, opioids were still heavily stigmatized, and opioid-addicted individuals seeking recovery were unable to gather for peer support without the risk of police surveillance. In fact, known drug users were already subject to arrest for "internal possession" [22], and loitering laws further prevented opioid-addicted individuals from connecting with one another. Moreover, one of the founders of AA, "Bill W," opposed individuals who had primary drug problems other than alcohol attending AA as he believed it would diminish drug-specific identification (i.e., with alcohol) and group cohesion, so early efforts to apply AA's model to opioids and other drugs were stymied [21].

Nonetheless, efforts to provide peer support for opioid-addicted individuals persisted beyond the 1930s. In 1947, an AA member named Houston Smith offered to start a group for drug-addicted individuals at the US Public Health Service Hospital in Lexington that was called "Addicts Anonymous" [21]. A patient by the name of Danny Carlson was one of the first to be admitted to Lexington in 1935, and he was subsequently discharged and readmitted eight times over the next 13 years [21, 22]. In 1948, Danny started attending Addicts Anonymous meetings, and after experiencing a spiritual transformation, he left Lexington and held the first Addicts Anonymous meeting in New York City in 1949. He changed the group's name to "Narcotics Anonymous" so that the group acronym, "AA," would not be confused with Alcoholics Anonymous, the "other" AA group [21, 22]. The group that Danny started, however, did not evolve into the Narcotics Anonymous that is known today [21, 22]. Though the New York NA group continued to meet through the 1970s, it ultimately dissolved, and its name was the only part of the group that would remain [21].

A few years after the first New York NA meeting, a man named Jimmy Kinnon formed a group that held its first meeting in California in 1953, and that was also called Narcotics Anonymous [21, 22]. Unlike the New York NA, the California group adapted AA's Twelve Steps and Twelve Traditions for use among NA members. Many of the early California NA members, including its founders, also attended AA and were known as "bridge members" who attended both AA and NA [9]. The early years of the California NA group were marked by inconsistent meetings, shifting leadership, and wavering ideology that created strife among members and threatened the group's existence [21, 22]. After nearly fizzling out entirely

in 1959, Jimmy Kinnon and other prominent NA members gathered and worked to not only save the group but also to reinvigorate it [22]. This involved, in part, solidifying the group's adherence to the 12-Steps and Twelve Traditions [22]. Their efforts worked. After nearly falling apart, NA grew from 5 meetings in 1964 to 225 meetings in 1976, to 2955 meetings in 1984, to 19,000 meetings in 1993, to over 43,900 in 2007 [22]. Today, the group holds over 67,000 weekly meetings across 139 countries [23].

Over time, the group began to see more female and white members, as well as an increased duration of abstinence (e.g., from 7.4 years in 2003 to 9.1 years in 2007 [22]). At present, NA's membership survey shows that its members are predominately white (79%) and male (59%, female: 41%) and vary in age: 21 years and younger (1%), 21–30 years (11%), 31–40 years (21%), 41–50 years (24%), 51–60 years (29%), and 60 years and older (14%) [23]. The survey also reports that the average duration of abstinence is 8.3 years, with members reporting up to 1 year (8%), 1–5 years (27%), 6–10 years (18%), 11–15 years (12%), 16–20 years (10%), and over 20 years (25%) of abstinence or, in NA's vernacular, "clean time" [23].

Due to the fact that NA adapted AA's Twelve Steps and Twelve Traditions for its group, AA and NA are largely similar in their structure and theoretical orientation. One notable difference between the two groups, however, is that rather than modifying the 12 steps to replace "alcohol" with "drugs," NA decided to replace "alcohol" with "addiction" to demonstrate its openness to those struggling with drugs *and* alcohol p16. Beyond this distinction, the groups share many similarities. For example, like AA, NA views addiction as a disease and their mission is to "provide an environment in which addicts can help one another stop using drugs and find a new way to live" [24]. Just as AA has embraced the notion of being fully financially self-supporting declining outside monetary contributions—espousing a vow of "corporate poverty" [25]—NA also made the commitment to be self-supporting, refusing to seek or take outside donations, and accepting instead only small donations from members themselves [24, 26, 27].

The sole membership requirement for NA is a desire to stop using alcohol and other drugs, and like AA, NA has 12 steps and 12 traditions, ("traditions" are the group's organizing principles and policies regarding internal operations at the group and national levels as well as policies on public relations) views recovery as a spiritual process, and endorses complete abstinence [21, 24]. The latter characteristic has raised a point of contention among the organization and its members, however, as some argue that "complete abstinence" is not possible while individuals are receiving medication-assisted treatment (MAT), particularly agonist therapy (e.g., methadone; buprenorphine). Though the organization contends it has "no opinion on outside issues, including prescribed medications" [24], NA also states that "Each group is free to make its own decision on recovery meeting participation and involvement in group services for those receiving medication assistance for drug addiction" [28]. NA acknowledges that allowing individual groups to decide their stance on medication-assisted treatment may limit NA participation for certain individuals [28], but nonetheless, still maintains that it neither supports nor opposes any

issues including this one. Challenges surrounding NA's stance on medication-assisted treatment will be further discussed later in the chapter.

SMART Recovery

SMART Recovery grew out of a predecessor, Rational Recovery (RR), which was founded by Jack Trimpey in the late 1980s [21, 26]. Trimpey strongly opposed AA and many of its defining features, particularly its spiritual orientation and view of addiction as a disease. In response, he created RR, a group inspired by Albert Ellis' Rational Emotive Behavioral Therapy (REBT), wherein recovery was viewed as a process driven by individual self-control, rather than peer support and spiritual experiences [26]. In a move that is unique to RR in the world of MHOs, Trimpey divided RR into two parts consisting of a nonprofit organization, the Rational Recovery Self-Help Network, as well as a for-profit organization, Rational Recovery, which was designed to provide professional addiction services. However, the Rational Recovery Self-Help Network split from the RR organization in the early 1990s and changed its name to "Self-Management and Recovery Training," known today as "SMART Recovery" [27].

The goal of SMART Recovery is to "support individuals who have chosen to abstain, or are considering abstinence from, any type of addictive behavior (substances or activities), by teaching how to change self-defeating thinking, emotions, and actions; and to work towards long-term satisfactions and quality of life" [26, 27, 29]. Thus, while not specifically focused on opioids, it welcomes individuals suffering from opioid use disorders. SMART Recovery has a cognitive-behavioral orientation and is committed to promoting evidence-based practices, stating that the group will "evolve as scientific knowledge evolves." In recent years, this has included advocating for the "appropriate use of prescribed medications" [29], an arguably attractive feature to those who may have experienced, or heard reports of, discrimination in 12-step groups against members using medication-assisted treatment, particularly agonist medication (e.g., see [30]). However, SMART Recovery does not outwardly oppose AA and other 12-step groups like its predecessor, RR, did. In fact, SMART Recovery recognizes that some of its members may choose to attend both SMART and 12-step groups and does not view the two organizations as mutually exclusive, despite having different theoretical orientations [29]. It is perhaps not surprising then that as many as 85% of SMART Recovery members attend both AA and SMART Recovery meetings, and, that despite the group's secular orientation, 60.7% of SMART Recovery members report believing in a God or higher power [11, 26, 31].

The goal of SMART Recovery is for its members to acquire the skills and techniques to abstain from addictive substances and behaviors and to obtain a balanced lifestyle [26, 29]. With the belief that addictions are complex maladaptive behaviors that people can resolve using self-directed change, SMART Recovery teaches members how to cope with urges to use addictive substances and/or behaviors [26, 29]. SMART Recovery meetings are therefore didactic and led by trained facilitators,

characteristics that distinguish the organization from other MHOs, which are not led by formally trained facilitators. Although this likely increases adherence to the SMART Recovery model and provides some degree of standardization and "quality assurance" across groups, the use of trained facilitators may also limit the group's growth, as training (and its associated financial cost) may be a barrier for some communities [26, 29]. Nonetheless, SMART Recovery currently holds over 1640 weekly meetings in the United States and a total of 2800 weekly meetings across 23 countries worldwide [32].

A recent systematic review of SMART Recovery [33] revealed a somewhat broad range of demographic characteristics among its members. With the exception that participants across studies were predominately white and had co-occurring mental health problems, participants ranged in age (average: 34–51 years), gender distribution (39–71% male), and proportion employed in either part- or full-time positions (31–63%). The eight peer-reviewed studies and four unpublished dissertations included in the systematic review used various participant samples (e.g., custodial offenders, dual-diagnosis participants, etc.) which likely account for some of the differences in sample characteristics [26]. As explained more below, the quality of the evidence for SMART Recovery is low and more research is needed to determine SMART Recovery's ability to influence adaptive change.

LifeRing Secular Recovery

The origin of LifeRing Secular Recovery can be traced back to the mid-1980s [21, 26]. Initially seeking help for his addiction at AA, James Christopher was turned off by its spiritual orientation, emphasis on a higher power, and conceptualization of addiction as a disease. Christopher decided to create a new, secular, abstinence-based organization that views addiction as an illness comprised of psychological, biological, and genetic factors. He held the group's first meeting in 1986 in North Hollywood, California, and called it "Secular Organization for Sobriety" or "Save Our Selves" (SOS). In SOS, there are no clearly defined steps to sobriety for its members. While encouraged to use other members' experiences as guidance, individuals are ultimately responsible for forging their own paths to recovery. Little is known about SOS members and there is no research on the group's effectiveness. The largest survey of SOS members to date is from 1996 [34], includes only 158 participants, and carries a low (15–29%) response rate. Based on this limited evidence, SOS members appear to be primarily male, Caucasian, nonreligious, and well-educated [34].

SOS still exists as an independent organization today, but, in 1999, a legal issue over its name led the largest SOS chapter to break off and establish itself as its own organization, LifeRing Secular Recovery [21, 26, 35]. As its name suggests, LifeRing Secular Recovery has a secular recovery model and, much like SOS, emphasizes the importance of an individualized, self-charted path to recovery. LifeRing Secular Recovery conceptualizes the path toward recovery as an endeavor wherein members are responsible for weakening their "Addict Self" and

strengthening their "Sober Self" [36]. Strengthening the sober self involves three components: recognizing the existence of the sober self and its role in leading the individual to his or her current place in life ("recognition"), facing recovery-related challenges and living a sober life ("activation"), and developing a "Personal Recovery Program" ("mastery") [35]. The organization's workbook, *Recovery by Choice*, can help members develop their Personal Recovery Program (PRP) across nine recovery-related domains [11, 37]. Conversely, members can opt to develop their PRP more organically, without the aid of the group's workbook.

Much like SOS, little is known about LifeRing, its members, and its effectiveness. A LifeRing membership survey from 2005 (N = 401) [36, 38] reveals that members are primarily Caucasian and well-educated (83% attended some college or junior college) and that 83% are between 30 and 65 years old (average age: 47.8 years), with fewer than 5% below the age of 30. Approximately one-third of members reported attending both LifeRing and AA, and nearly half (45%) of participants reported being diagnosed with a co-occurring mental illness. A 2013 LifeRing Membership survey [16] was similar to its 2005 counterpart in that participants (N = 380) were predominately white (95.9%) and well-educated (some college: 23.4%, associate degree: 7.7%, undergraduate degree: 24.9%, graduate degree: 36.2%), but there were no questions that assessed co-occurring mental health conditions. The most common "drug(s) of choice" were alcohol (96.3%), marijuana (14.5%), methedrine/methamphetamine (7.1%), prescription painkillers (6.8%), and cocaine (powder: 6.3%). Over three quarters (77.2%) of participants reported having attended "abstinence-based recovery programs" in the past, with 87.8% of respondents reporting that they had attended AA [16]. Approximately one-third of participants reported that they currently attend other "abstinence-based recovery programs," with 57.1% of those respondents attending 12-step groups [16].

Celebrate Recovery

Unlike the founder of LifeRing, who was turned off by AA's emphasis on spirituality, the founder of Celebrate Recovery, John Baker, sought a more overtly religious, Christian-focused MHO experience than what he found in AA [26]. Following a reported vision from God, Baker wrote to his pastor, Rick Warren, about his vision and plan for Celebrate Recovery [39]. Warren gave his blessing for the group, and Baker held the first Celebrate Recovery meeting in Saddleback Church in California [11, 39].

Although Celebrate Recovery's structure is based on that of 12-step groups, there are several notable differences between the organizations. For example, Baker built upon the 12-steps by adding biblical comparisons to each step (e.g., "2. We came to believe that a power greater than ourselves could restore us to sanity. *For it is God who works in you to will and to act according to his good purpose. Philippians 2:13 NIV*") [39]. He also created the group's "Eight Recovery Principles" that provide further scripture-supported guidance toward recovery (e.g., "Happy are those who mourn, for they shall be comforted" and "Happy are those who know that they

are spiritually poor") [39]. Moreover, Celebrate Recovery members are encouraged to have individual sponsors, who, while similar to AA sponsors, differ in that they place a particular emphasis on spiritual growth [11, 26]. Moreover, members are encouraged to have "accountability partners" who are at a similar stage in their recovery and who, between meetings, can provide extra support through shared experiences and prayer [11, 26].

Celebrate Recovery is not specific to opioid use disorder, instead it is open to any individual struggling with addiction or other patterns of behavior, such as codependency and eating disorders [26, 39]. Since its first meeting in 1991, Celebrate Recovery reports that it has now grown to over 35,000 churches worldwide, and holds meetings also in recovery houses, universities, prisons, and rescue missions [39]. Information regarding the individuals who make up the group's membership base is not available, however.

Recovery Coaching

Within the spectrum of peer-based recovery support services, Recovery Coaching has emerged as a growing and popular peer-to-peer delivered service that is being integrated into existing addiction treatment and recovery-oriented systems of care [40]. Recovery Coaches are people who themselves are in recovery from a substance use disorder and/or other mental health conditions. Drawing from a combination of experiential knowledge and specialized strength-based training, Recovery Coaches guide and mentor others into sustained, long-term recovery [41, 42].

Recovery Coaching is conceptually rooted in the notion that social support facilitates recovery by helping individuals build "recovery capital," the internal and external resources needed to initiate and maintain recovery [43, 44]. Greater accrual of recovery capital may support continued remission by building an individual's resilience and ability to cope, thereby helping to buffer and reduce stress [44]. Peer recovery support services can also provide the four types of social support identified in the literature: emotional, informational, instrumental, and affiliational [45]. Peers receiving social supports, in turn, may experience increased self-esteem, hope, and confidence (emotional); receive life or skills training (informational) or concrete assistance (i.e., with housing or transportation; instrumental); and are connected to the others in the recovery community (affiliational) [46, 47]. Coaches serve as "recovery catalysts" who help peers develop and manage their own recovery plans through motivation, empowerment, and linkages to formal and informal resources necessary to facilitate recovery, including connections to housing, employment, professional services, and community supports [41, 48].

Training and Accreditation

Recovery Coaches are trained in the science of addiction, the recovery process, stages of change and recovery, and various pathways to recovery, understanding of personal biases, ethical, and boundary issues, and development of skills in building

relationships, self-disclosure, and helping peers develop personalized pathways to recovery [49]. Core competencies are based on the principles, as identified by the Substance Abuse and Mental Health Services Administration (SAMHSA), that a Coach-peer relationship is recovery-oriented, person-centered, voluntary, relationship-focused, and trauma-informed [50]. Certification programs may also offer trainings in additional topics, including motivational interviewing techniques, ethical considerations, cultural competency, and skills for specific delivery settings or special populations (such as medication-assisted treatment) [51]. Recovery Coaches work in paid or volunteer positions [48] and receive ongoing supervision

Training and certification requirements for Recovery Coaches differ from state-to-state and between organizations. Required hours of training range from 30 to 100, while hours of volunteer or work experience range from 0 to over 500 h. Many states use the Recovery Coach Academy, a 5-day curriculum developed by the Connecticut Community for Addiction Recovery (CCAR), as the standard training program to certify Recovery Coaches [49]. To date, 40 states offer certifications for mental health peer support specialists, 13 of which offer certifications specifically for substance use disorder Recovery Coaches [51, 52]. As peer Recovery Coaching becomes more integrated into the evolving landscape of addiction treatment and recovery, it is imperative that peer supports are held to a high-quality standard. An accreditation system must be established to ensure that peer recovery support workers, including Recovery Coaches, are qualified and recovery-oriented and meet ethical and legal considerations [46, 53].

Recovery Coaching Settings

Recovery Coaching can be delivered through a range of service settings and organizational contexts, and can, therefore, be adapted to serve individuals at varying stages in recovery and who are on different recovery pathways [47]. For example, individuals may benefit from receiving Recovery Coaching prior to recovery identification and initiation of treatment (to strengthen motivation), as an adjunct to formal treatment, following treatment (recovery maintenance and relapse prevention). For those who cannot or do not wish to enter a formal treatment program, Recovery Coaching provides an option that is separate from specialized, professional treatment programs altogether. Nonprofit, peer-run recovery community centers, faith-based institutions, social service agencies (i.e., child welfare system, HIV/AIDS service centers), recovery residences, criminal justice settings (drug courts, jails or prisons, probation or parole programs), and behavioral health and primary care or hospital settings also utilize Recovery Coaches [46]. Thus, Recovery Coaching can be used on its own or in conjunction with professional treatment and/or various other peer-support services (e.g., mutual-help organizations) and organizations.

In terms of their organizational context, Recovery Coaches may work in free-standing recovery community organizations or within a host agency that provides adjunct treatment or social services. The unique service and organizational settings in which Recovery Coaches operate may determine the populations they serve (who may have specific service needs), their treatment status and

severity, and, operationally, how the position is supervised and funded (i.e., through federal or state grant funding, private pay, insurance reimbursement) [47]. Depending on these variables, the position may be referred to by other job titles, including recovery mentor, guide, or peer resource specialist. The titles are interchangeable, but all emphasize a community-based model of peer support, provided by an individual who has the experiential knowledge to assist others [47, 54].

Medication-Assisted Recovery Coaching Support

Within the context of treatment for opioid use disorder, a specific need exists for recovery support for patients receiving medication-assisted treatment. In 1988, the National Alliance for Medication Assisted Recovery (NAMA Recovery, www.methadone.org) was established in response to growing issues faced by OUD patients receiving methadone treatment and was later expanded to include all forms of MAT. NAMA Recovery is a recovery advocacy organization, composed of thousands of MAT patients, friends, family, community members, and healthcare professionals, with the objective of providing education to patients, providers, and the general public in order to change public perceptions of, and advocate for, MAT [55]. NAMA also offers a national training and certification program for the role of Certified Medication-Assisted (CMA) Treatment Advocate to specifically support the goals of methadone advocacy. Individuals certified by NAMA support the goals of methadone advocacy, abide by the Code of Ethics, and take the Patient Advocate Certification course licensed by the New York State Office of Alcoholism and Substance Abuse Services (OASAS) for 7 h of course credit for Credentialed Alcoholism and Substance Abuse Counselor (CASAC).

Through a collaboration with the Albert Einstein College of Medicine, the Medication-Assisted Recovery Services (MARS) Project was established in 2005 as a structured, peer-initiated and -based recovery support project specifically for the needs of the medication-assisted recovery community. MARS, staffed by patients currently or formerly receiving MAT, offers recovery support services to patients in MAT, including trainings in medication-assisted recovery and peer leadership and mentoring, support groups, and substance-free recreational/social activities. Its expansion began in 2012 through the formation of the Beyond MARS Recovery Coach Training Institute, which provides training and educational services to treatment programs in order to replicate the MARS model of integrating structured, peer-delivered recovery support into professional treatment [56]. Additionally, the MARS Project delivers a 30-h Recovery Coach Academy, developed by CCAR, and required to qualify for the New York State Certified Addiction Recovery Coach (CARC) credential [57].

Delineating the Role of a Recovery Coach from Mutual-Help Organization and Existing Professional Service Roles

Given the variability in service settings, organizational contexts, and recovery stages and pathways, Recovery Coaching's adaptability has inevitably led to some

ambiguity in its defining and distinguishing responsibilities [47]. Importantly, there has been significant emphasis on delineating the role of a Recovery Coach from those of existing professional treatment providers (e.g., counselors, clinicians, and addiction specialists) and 12-step sponsors (e.g., an AA or NA sponsor) [47, 54, 58]. While the role of a Recovery Coach positions itself between that of a sponsor and a professional treatment provider, it is not meant to replace or compete with, but rather to link to and support, these existing MHOs and traditional addiction treatment services. Recovery Coaches are *not* 12-step sponsors, therapists (i.e., do not provide counseling or therapy), healthcare providers (i.e., do not diagnose), or religious or spiritual leaders, but should refer peers to allied roles, when appropriate [54, 59].

A mutual-help, 12-step sponsor is a well-established, informal position which does not require any formal training. Sponsors articulate a singular pathway to recovery: helping sponsees understand and work through the 12-step framework. Sponsorship operates separate from professional treatment and is not reimbursable. Unlike a 12-step sponsor, a Recovery Coach is a specialized staff or volunteer worker who has received training and whose role functions within the context of a formal, structured service organization. A Recovery Coach may be bound to organizational guidelines and requirements, including a "caseload," duration of the coach-peer relationship, and where mentorship activities are conducted. Central to the tenets of Recovery Coaching is the emphasis that there are "many pathways to recovery"; Coaches help individuals through the recovery process by providing guidance relating to *multiple* recovery pathways and facilitating access to a wide range of recovery-related resources [54].

Professional treatment providers are formally educated, licensed, and/or accredited to provide clinical or medical services. In contrast, Recovery Coaches' credentials and ability to help others achieve sustained recovery is based principally in their own, lived recovery experiences [60]. Patients of professional treatment providers have often already reached the point of readiness to change. Recovery Coaches provide nonclinical, nonprofessional support to individuals across the recovery continuum, including those who are seeking recovery but may not yet have initiated a recovery attempt or made any contact with professional addiction treatment services or mutual-help organizations. Coaching may be provided in conjunction with or as an alternative to specialized, professional addiction treatment [54, 58]. Recovery Coaching is more intensive than professional treatment and case management, as Coaches make themselves accessible to peers and make efforts to accompany them to access other resources when needed. Nonetheless, current research has highlighted role ambiguity and boundary issues as a challenge faced by Recovery Coaches. A small, qualitative study to understand perspectives regarding an integrated Recovery Coach initiative in outpatient community-based substance use disorder treatment settings found that Coaches reported feeling discomfort and tension in trying to work collaboratively with the care team, and patients reported uncertainty as to the specific role played by the Recovery Coach as part of their care [61].

Research on Peer Support Models for Opioid Use Disorder

Effectiveness and Cost-Effectiveness of 12-Step Mutual-Help Organizations for Opioid Use Disorder

While hundreds of empirical studies have been conducted on AA and clinical treatments designed to facilitate AA participation during and following professional treatment (i.e., "Twelve-Step Facilitation" [TSF] interventions) [62–64], NA has received relatively little empirical attention regarding its effectiveness, and no studies have evaluated its mechanisms of behavior change. Among the studies that do evaluate NA's effectiveness, many evaluate 12-step groups (e.g., NA, Cocaine Anonymous (CA), AA) as a whole (e.g., [65, 66]), thereby precluding an examination of NA by itself. Moreover, many of the studies that evaluate NA (and other 12-step groups) focus on individuals who use stimulants (e.g., [67]), despite the fact that NA members report past regular use of a variety of substances, including 38% reporting past regular opioid use [23]. When considering that many countries are facing an opioid epidemic and that addicted individuals throughout the world attend over 67,000 NA meetings *per week*, these facts are perplexing [23]. By examining the research that does exist concerning NA and other 12-step groups, we will identify research gaps and suggest avenues for future research on this widely used resource.

Narcotics Anonymous conducts periodic membership surveys, providing some information about its members, their problem substances, and meeting attendance (e.g., [23]). Beyond this, few researchers have evaluated NA members, with the exception of Galanter and colleagues, who conducted a cross-sectional survey of 396 NA members to characterize those who are long-term members and primarily abstinent [68]. Galanter and colleagues found that, on average, participants were 27 years old when they first attended NA, and that the majority (87%) of participants had received prior treatment for a substance use disorder. Members self-reported that their primary substances were cocaine (28.5%), heroin (27.5%), other opiates (13.4%), methamphetamine (12.9%), alcohol (8.6%), marijuana (6.6%), and other stimulants (2.5%). Researchers noted that members who reported opioids other than heroin as their primary substance had, on average, a shorter membership duration and length of abstinence, and were significantly less likely to have been a sponsor when compared to those whose primary substance was cocaine [68]. This finding suggests that members' substance use histories, particularly their primary substances, may be an important factor when considering substance use outcomes and group participation and affiliation among NA members, and warrants investigation in future research.

Taking a step further, other researchers have evaluated the effect of 12-step attendance on substance use outcomes over a 5-year follow-up period following treatment. For example, Gossop and colleagues [65] evaluated the frequency of NA/AA attendance and substance use outcomes following residential treatment among a UK sample of drug-dependent participants, 77% of whom reported heroin use in the 3 months prior to treatment intake and had used heroin for an

average of 9.7 (*SD* = 5.6) years. About one-third (35%) of participants reported attending at least 1 NA/AA meeting in the 2 years prior to treatment, attending an average of 26.5 (*SD* = 46.2) meetings during that time. Researchers found that following residential treatment, participants who attended NA/AA were significantly more likely to be abstinent from alcohol and opioids at all follow-up points (1, 2, and 4–5 years after treatment). In fact, those who attended NA/AA were three to four times more likely to be abstinent from opioids and four to five times more likely to be abstinent from alcohol, relative to those who did not attend NA/AA. Researchers also found that those who attended NA/AA regularly (i.e., once or more a week) at some point during the follow-up were significantly more likely to be abstinent from opioids and alcohol at 4–5 years when compared to those who did not attend regularly. These findings suggest that NA/AA may be helpful recovery support services for drug-dependent individuals who have completed inpatient treatment, and, that while any amount of NA/AA attendance appears to be beneficial for opioids and alcohol use, regular weekly attendance can have positive, enduring impacts on abstinence after treatment. Though these findings are promising, additional research is needed to replicate this effect in other samples of individuals with opioid use disorder.

In an effort to further understand the effect of 12-step participation on drug use, Bog and colleagues [69] conducted a systematic review and meta-analysis of 12-step programs for illicit drug use. Researchers examined drug use both during and post treatment (i.e., at 6- and 12-month follow-ups) and found that when compared to "treatment as usual" or another psychosocial intervention (e.g., cognitive behavioral therapy [CBT]), TSF and 12-step participation were equally effective. Notably, more than half of the ten studies in the review included participants with cocaine use disorder, though a few studies included participants with opioid use disorder or an unspecified drug use disorder. Moreover, this review did not include studies that compared 12-step or TSF to a 12-step or TSF variant (e.g., [66]), though it is unclear the degree to which the "treatment as usual" comparison conditions included 12-step principles or recommendations to attend 12-step groups (although it is likely to be high as the majority of US SUD programs strongly facilitate 12-step MHO participation).

By omitting studies that compared 12-step or TSF to a 12-step or TSF variant, the Bog et al. [69] review did not take into account studies that highlight some of the more nuanced effects of 12-step participation on illicit drug use. For example, Crits-Cristoph and colleagues [67] in the Collaborative Cocaine Treatment Study found that individuals with primary cocaine dependence who were randomly assigned to receive individual group counseling (IGC) + group drug counseling (GDC)—both of which were based on TSF principles—had significantly fewer days of past 30-day cocaine use and better Addiction Severity Index drug use composite scores (demonstrating a reduction in drug-related problems) at 12-months posttreatment, when compared to those who received GDC + cognitive therapy or GDC + supportive-expressive therapy. Furthermore, at 12-months posttreatment, those in the TSF-based IGC + GDC group were significantly more likely to have one continuous month of abstinence when compared to those who received GDC + cognitive

therapy or GDC + supportive-expressive therapy, with a similar pattern of results for two and three consecutive months of abstinence [67]. Together, these results suggest that patients who receive TSF in both individual and group settings have better substance use outcomes than those who receive group-based TSF and either individual cognitive therapy or supportive-expressive therapy, the former of which (cognitive therapy) is often considered the "gold standard" for treatment.

Also important when considering the efficacy of 12-step participation and TSF is the use of medication treatment. Studies examining the effect of 12-step participation or TSF in *addition* to medication treatment on substance use outcomes have yielded mixed results. For example, in a sample of individuals diagnosed with prescription opioid dependence, researchers found that participants who received opioid drug counseling (ODC; which included discussion of the benefits of 12-step groups) in addition to standard medical management (SMM) and buprenorphine-naloxone did not have better substance use outcomes (i.e., higher rate of abstinence) when compared to those who received SMM and buprenorphine-naloxone only [70]. Moreover, White and colleagues [71] found no association between abstinence and past year 12-step meeting attendance among a sample of participants receiving methadone maintenance treatment (MMT). Conversely, however, Monico and colleagues [72] found that in a sample of buprenorphine maintenance treatment (BMT) patients, participants who were abstinent at the 6-month follow-up had attended significantly more NA meetings than those were not abstinent. In fact, researchers found that each additional meeting participants attended was associated with increased odds of being abstinent at 6 months, and of BMT retention [72].

Beyond the associations themselves, these latter findings are particularly intriguing given reports of discrimination at 12-step meetings against individuals who use medications for opioid use disorder (e.g., [30, 72]). For example, among this particular sample of participants, only one-third (33%) of participants reported that they had disclosed their BMT status to another NA member and that among that subset of participants approximately one quarter (26%) had reported that someone at NA had encouraged them to decrease their dosage or stop BMT [72]. Similarly, White and colleagues [30] found that approximately one-third (34%) of MMT participants disclosed their MMT status with another NA/AA member and that about a quarter (24.4%) of the sample overall reported one or more negative responses to their MMT status (e.g., were not allowed to be a sponsor, were not allowed to speak at meetings, were encouraged to reduce their methadone dose, were encouraged to stop taking methadone, etc.). When considering that nearly the same proportion of participants in both studies chose to disclose their medication status (approximately one-third), and experienced negative reactions to their medication status (approximately one quarter), the question of why one study found an additional benefit of 12-step participation [72], while the other did not [30], is intriguing. Perhaps the answer is due to a simple methodological difference, or perhaps it is something more. Do patients taking methadone experience a more enduring form of discrimination when compared to buprenorphine-naloxone patients? Is there someone or something acting as a social buffer for one group of participants, but not for the

other, or were there differences in the acceptance of agonist medications among the different groups in different geographical regions where the studies were conducted? Or perhaps there are differences in the individuals' drug use history, substance use severity, or some other participant characteristic that sets the groups of participants apart?

Indeed, there are myriad avenues for future research on opioid use disorder; however, the intersection of 12-step participation and medication treatment is likely a fruitful juncture at which to begin. Recent findings have highlighted the positive and enduring effects of medication treatment on opioid use (e.g., [70]), and emerging evidence has pointed toward the positive effects of 12-step participation on opioid use (e.g., [65]). Also, the Hazelden Betty Ford Foundation, historically the originator of the TSF model of care, has incorporated buprenorphine/naloxone treatment into its 12-step approach (known as the "CORE-12" program) to try to enhance outcomes among its opioid use disorder patients. Outcome data are not yet published but unofficial reports appear promising; it, therefore, seems plausible that there is a potential opportunity for synergy between these two valuable treatment options. Although researchers have already begun to examine this potentially synergistic relationship (e.g., [70–72]), the question must be further explored with greater consideration for potentially moderating factors, such as discrimination in 12-step groups. For it also seems plausible that medication treatment and 12-step participation could serve as two opposing forces, with potentially deleterious effects. For example, might a medication treatment patient who is attending NA and experiencing social pressure to reduce or stop their treatment decide to stop attending 12-step groups, or to stop taking their medication, or worse, to stop both? Finding ways to bolster, rather than hinder, combinations of treatment and peer-support services, such as 12-step groups, for opioid use disorder will be crucial not only for improved substance use outcomes, but also potential cost-savings, which have been well-documented among individuals with alcohol use disorder who attend AA (e.g., see [73, 74]).

Research on Non-12-step Mutual-Help Organizations

As noted, while there are hundreds of studies on AA, and several on samples that included NA and AA or other 12-step group participation, there are very few studies on non-12-step MHOs such as Celebrate Recovery, LifeRing Secular Recovery, and SMART Recovery. Of the three groups, Celebrate Recovery has received the least amount of empirical attention and lacks systematic research on both its membership base and efficacy. Due to the fact that Celebrate Recovery is open to individuals who struggle with a range of problematic patterns of behaviors, research characterizing its membership base could help shed light on whether the group does indeed include members who struggle with issues other than substance use, or if the group is primarily comprised of individuals with substance use disorder, and, of these, what proportion has an opioid use disorder [26]. Examining and characterizing Celebrate Recovery's membership base could help identify future avenues of research concerning the group's efficacy.

Receiving slightly more attention than Celebrate Recovery is LifeRing Secular Recovery, which, beyond its own organization's membership survey, has only recently been the subject of formal research on non-12-step MHOs. Zemore and colleagues [75] conducted the first longitudinal study to evaluate substance use and related outcomes among individuals attending non-12-step MHOs (i.e., SMART Recovery, LifeRing Secular Recovery, and Women for Sobriety). Both 12-step and non-12-step group members were surveyed at baseline and at 6 and 12 months. Although researchers found Women for Sobriety, LifeRing Secular Recovery, SMART Recovery, and 12-steps groups to be equally as effective, participants who affiliated with Women for Sobriety had lower odds of total abstinence. Moreover, when compared to 12-step members and after controlling for covariates, researchers found that participants who identified SMART Recovery as their primary group at baseline had significantly worse substance use outcomes (e.g., relating to total abstinence, alcohol abstinence, and alcohol problems) at follow-up. This difference was no longer evident, however, once researchers controlled for baseline abstinence status, which ranged from controlled substance use to complete, lifetime abstinence [26, 75]. Researchers posit that individuals with less comprehensive abstinence goals may self-select into SMART Recovery and LifeRing Secular Recovery, a notion that could be explored in future research. It is important to note that this study focused on individuals who had a lifetime diagnosis of alcohol use disorder, and not opioid use disorder, although many participants also had a history of drug use. In order to better understand the efficacy of non-12-step groups for a range of individuals with substance use disorder, future research comparing 12-step groups to non-12-step groups should include individuals with a history of a primary opioid or other drug use disorder.

Most of the research on non-12-step groups has focused on SMART Recovery, though little quality research exists on this group and none has focused on opioids. Evidence suggests that members find meetings to be helpful to their recovery [76] and that the group experience and cognitive behavioral tools [12] that members acquire are also beneficial [26]. In a recent systematic review that contained only one randomized controlled trial (RCT), researchers examined the effectiveness of SMART Recovery [33]. The single RCT included in that review examined the effect of participation in SMART Recovery on substance use and related outcomes by randomizing participants to three conditions, in which they participated in (1) face-to-face SMART Recovery meetings only, (2) Overcoming Addictions, a web-based program that is based on SMART Recovery principles, only, or (3) a combination of face-to-face SMART Recovery meetings and Overcoming Addictions [26, 77]. Participants in all three groups overall showed improvement on drinking-related outcomes (i.e., drinks per drinking day, percent days abstinent, and alcohol-related problems) at the 3-month follow-up. However, when examined more closely, important group differences emerged. For example, whereas the SMART Recovery group demonstrated improvement in substance-related outcomes between the 3- and 6-month follow-ups, both the Overcoming Addictions only and SMART Recovery + Overcoming Addictions groups regressed. Between the 3- and 6- month follow-ups, 66% of participants in the Overcoming Addictions only group attended zero

meetings, and the overall average number of meetings attended dropped from 5.9 to 3.0 online meetings [26, 77]. Interestingly, however, a higher proportion (78%) of participants in the SMART Recovery only group reported attending zero meetings between the 3- and 6-month follow-up, resulting in a decrease in the average number of in-person meetings attended, from 3.2 to 1.9 meetings. This finding suggests that even with low levels of meeting attendance, SMART Recovery may have positive, enduring effects on alcohol use outcomes, though more research is needed to examine the long-term outcomes of individuals who attend SMART Recovery [26, 77]. Again, however, these studies assessed alcohol use and not opioid use disorder. There is a dearth of information on the utility of SMART Recovery for those with opioid use disorder.

The abovementioned studies demonstrate that researchers are working toward a better understanding of non-12-step groups, their efficacy, as well as their potentially unique value for individuals with substance use disorders who are seeking an alternative to 12-step groups. Overall, however, research is needed to explore and delineate the bounds of these resources for individuals with substance use disorder, and in particular, for those with opioid use disorder.

Research on Recovery Coaching Models

A small but growing evidence base shows support for the effectiveness of Recovery Coaching for individuals in or seeking recovery from substance use disorders. Two systematic reviews, published between 1994 and 2014, concluded that individuals who participated in Recovery Coaching showed reductions in substance use, improvements in recovery-related outcomes, or both [78, 79].

Four randomized controlled trials were identified in the systematic reviews. However, the peer recovery support interventions were widely variable, delivered in various settings, and, for the purposes of this chapter, none examined the effects of a peer support intervention for a sample with primary opioid use disorder. The first RCT that included a peer recovery support intervention randomly assigned a sample of 1175 out-of-treatment adults with past 90-day cocaine and/or heroin use receiving general medical care at urban hospital walk-in clinics to receive one of two interventions: a one-time, brief, peer-delivered motivational/education intervention with a "booster" follow-up phone call, written advice and a referral list (experimental condition); or, written advice and a referral list only (control condition). At the 6-month follow-up, the intervention group was significantly more likely to be abstinent from cocaine and trended towards greater heroin or combined cocaine and heroin abstinence [80]. Another RCT examined the effectiveness of adding "Citizenship Training"—a weekly peer support intervention delivered over a 4-month period—to professional treatment in a sample of 114 outpatient adults with severe mental illness and criminal charges within the past 2 years. Thirty-one percent of participants had an alcohol use disorder (AUD) and 42% had another substance use disorder (SUD). At the 6- and 12-month follow-ups, the intervention group showed a significant reduction in alcohol use while the control group

demonstrated a significant increase in alcohol use over time. Participants from both conditions exhibited similar significant decreases in other substance use and in criminal justice charges [81].

Tracy and colleagues [82] conducted an RCT to examine the effects of a completely peer-driven support program, which included individual support/mentoring, peer-led groups, and escorting the patient to their first outpatient program, in a sample of 96 veteran inpatients receiving treatment for substance use and/or psychiatric treatment, 88% of whom had an AUD or SUD with psychiatric comorbidity. Patients were randomly assigned to one of three conditions: (1) treatment as usual (TAU; control); (2) TAU + peer support; or, (3) TAU + peer support + a clinician-delivered, dual recovery relapse-prevention therapy. Compared to TAU, both experimental conditions which added a peer recovery support component were associated with significantly higher rates of post-discharge treatment adherence for outpatient substance use as well as for substance use, general medical and mental health services combined [82].

Lastly, O'Connell and colleagues [83] conducted an RCT which randomized 137 adults with co-occurring psychosis and SUD post-discharge from a mental health center to 3 conditions: TAU + outpatient service transportation vouchers (control), TAU + transportation vouchers + skills training, and skills training + a peer-led social engagement program, which included a peer in recovery who made home visits and accompanied patients to mutual help organizations. Patients in both experimental conditions had significantly greater decreases in past-30-day alcohol use at 3 months when compared to those receiving treatment as usual, and this effect remained significant at 9 months for those in the peer support intervention. The addition of peer-led support also resulted in other improved recovery-related outcomes, including relatedness, self-criticism, and outpatient service use [83].

Research has also shown promising outcomes for an integrated Recovery Coaching model for parents diagnosed with substance use disorder in the child welfare system [84, 85]. Parents with substance use disorders who had been randomly assigned to a Recovery Coach had a significantly greater likelihood of reunification with their child within 3 years of foster placement (21% vs. 16%). Notably, early access (within 2 months) to substance use services had a significant effect on the likelihood of reunification *only* when parents were connected with a Recovery Coach (22% vs. 14%) [85]. The integrated Recovery Coaching model – wherein Coaches assisted parents with obtaining needed treatment services, provided outreach efforts to support treatment engagement, and helped with concurrent permanency planning – also suggests subsequent indirect effects on child outcomes. In a study of 453 families which randomized mothers to the Recovery Coach intervention, children whose mothers had received the intervention were significantly less likely to be associated with a subsequent juvenile arrest after having returned home from foster care (9% vs. 19%) [84].

Results from these RCTs are supported by additional studies, which used pre-post, quasi-experimental, and cross-sectional study designs, and found that peers who experienced some form of a Recovery Coach intervention demonstrated positive outcomes for improved relationships with treatment providers

[86, 87], increased treatment adherence/retention [88–90] and satisfaction [91], improved access to social supports [87, 92], improved housing stability [93], decreased severity of depression and anxiety symptoms [94], decreased criminal justice involvement [88, 93, 95], reduced rates of relapse [92] and re-hospitalization [95, 96], and reduced substance use [88, 90, 91, 94, 95, 97]. Although the existing data is promising, results are difficult to generalize across the range of delivery settings, populations, and measurable outcomes. No studies to date have specifically evaluated outcomes of Recovery Coaching for patients with opioid use disorder.

With regard to patients with opioid use, emerging research has shown promise for incorporating Recovery Coaching into hospital emergency departments (EDs). Samuels and colleagues [98] conducted a retrospective study to evaluate the implementation of a Recovery Coaching consultation and naloxone distribution program for patients with opioid-related visits at two Rhode Island hospital EDs. In this program, ED physicians could order a Recovery Coach consultation, and Coaches would arrive within 30 min to provide patients with support, naloxone education, and referral to addiction treatment. Coaches would also follow up with patients after their ED visit. Electronic medical records (EMRs) for 555 patients who had been treated and discharged from the ED after an opioid overdose (49.1%), or who were identified as having opioid misuse or opioid use disorder, were reviewed pre-, post-, and 1 year following the program implementation. Following implementation of the program, one-third of patients received a consultation with a Recovery Coach, most of whom also received take-home naloxone (88.9%). Discharge with a referral to treatment increased significantly from 9.3% to 20.7%.

Clinical and Policy Implications of the Science of Peer Support Models for Addressing Opioid Use Disorder

Peer support models like MHOs provide an extensive network of recovery-focused social peer support, available mostly free of charge in most US communities. Individuals are able to self-regulate the intensity of their involvement in these entities over the long-term, according to their own perceived need for as long as is desired. Thus, these models form an adaptive and highly cost-effective community-based social support network [13, 99]. Because alcohol is the predominant drug accounting for the majority of addiction cases in the United States and in most middle- and high-income countries globally, and AA is by far the biggest and most influential MHO, most of the research to date has been conducted on AA and related clinical interventions designed to facilitate participation in AA (i.e., Twelve-Step Facilitation interventions [100]). It is currently unclear, however, whether the strong clinical, public health, and cost, benefits observed in the research on AA and related 12-step clinical treatments [27, 100] are similarly observed among those with opioid use disorders attending NA, AA, or other 12-step MHOs. More research of all types is clearly needed in this regard given that NA, like AA, is a freely available and ubiquitous recovery specific community resource.

Emerging research on the utility of MHO peer support for opioid use disorder in combination with medication treatment highlights the challenge of engaging OUD patients who receive medication treatment in 12-step MHOs (i.e., NA), which, despite their successful track record of engaging and helping people with OUD, have historically held an anti-medication stance. NA is beginning to soften its stance on medication use and appears to be more welcoming of members with opioid problems who are on medications such as buprenorphine/naloxone [28]. While there appear to be additive or synergistic therapeutic effects among participants on buprenorphine/naloxone who attend NA [72], more research is needed to understand the barriers to and benefits of combining 12-step participation and medication treatment. It is also unclear whether NA will remain its own "abstinence-based" pathway for those who want a medication-free path to recovery, or whether it will adapt to accommodate more fully those who are taking agonist medications to aid their recovery. It may be that other MHOs, such as SMART Recovery, which is openly and warmly welcoming to individuals regardless of their medication use, may be a better option for those receiving medication treatment for opioid use disorder.

The utility of non-12-step MHOs is also unknown from a rigorous empirical standpoint, but their growth in numbers is one kind of evidence of their utility. As demonstrated by their staying power and growth, non-12-step MHOs are likely to be helpful for at least some segments of addicted populations. Again, however, we know very little regarding the formal clinical and public health utility of such organizations as they pertain to opioid use disorder. Similarly, there has been tremendous growth in peer recovery support services in formal treatment settings.

Stemming from research on MHO peer support, the Recovery Coaching model continues to gain momentum throughout the United States within an evolving system of SUD treatment. Current research on Recovery Coaches, albeit limited, suggests that people receiving peer recovery support from a Recovery Coach may experience better substance use and recovery-related outcomes. However, comparisons across studies are limited by methodological concerns, including varying (and often unclearly defined), definitions of Recovery Coaching, wide-ranging intervention models, populations served, and measurable outcomes, as well as a lack of comparison groups [78, 79]. Despite their growth, there is a critical need for research that employs rigorous methods (i.e., RCTs) to systematically characterize Recovery Coaching, identify "best practices," and examine its clinical, public health, and economic impact [53]. To begin, researchers should establish clear and consistent definitions of the Recovery Coach role, intervention, and measurable outcomes; isolate the specific therapeutic effects of Recovery Coaching from those of other peer recovery support services delivered simultaneously; and, examine long-term recovery-related outcomes in a generalizable sample of primary SUD patients. Studies should examine the effectiveness of specific Recovery Coaching elements, such as: the delivery setting (clinical or community-based), organizational context (free-standing RCO or integrated within a treatment agency), the individual's recovery pathway and treatment stage (i.e., parallel, sequential, or in lieu of treatment), and the professional training of the Recovery Coach. Overall, the research agenda

must address the key questions of if, how, and for whom Recovery Coaching may contribute to recovery-related outcomes.

Overall, the burden of disease, disability, premature mortality, and economic toll confer a prodigious and worrisome strain on US society. Although professional treatment efforts have expanded and are considerable, there is a recognized need for any and all resources to be brought to bear to mitigate the increasing burden of opioid use. The MHO and peer support networks that have emerged in the United States are valuable and cost-effective resources that may aid recovery and support long-term remission for those with opioid use disorder (e.g., [65]). As with all types of services, questions remain as to which types of peer supports are necessary and best-suited to which individuals, at what point, over what period, and at what cost. These are all questions that await further empirical investigation as we endeavor to expand treatment options and availability for individuals with opioid use disorder.

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Harm Reduction Approaches for Opioid Use Disorder

8

Sarah E. Wakeman

Introduction

An estimated 15.5 million people have an opioid use disorder across the globe [1]. In 2015, there were more than 190,000 drug overdose deaths worldwide, predominantly due to opioids, and 12 million people who were actively injecting drugs. Of these, 1.6 million had human immunodeficiency virus (HIV), 6.1 million had hepatitis C, and 1.3 million were coinfected with HIV and hepatitis C [2]. In the United States, the toll of untreated opioid use disorder has led to an epidemic of overdose deaths resulting in a decline in life expectancy over the past three years [3]. While expanded access to effective treatment is a crucial response to the ongoing crisis of opioid-related harms, less attention and funding have gone toward harm reduction strategies. An outsized focus of the response to opioid use continues to center on supply reduction. Expansion of the existing treatment system or further criminal justice efforts to reduce drug use may not target the needs of people who are actively using drugs and at highest risk of harm or death. In contrast, harm reduction offers a practical approach which is "informed by the social and structural realities of drug use" and focuses on reducing negative consequences and improving the lives and health of people who use opioids [4].

Overview of Harm Reduction

Harm reduction is an approach which aims to reduce the harms associated with drug use, recognizing that despite efforts at prevention and treatment some people will continue to use drugs. A defining feature of harm reduction is a focus on minimizing

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harm, rather than necessarily reducing drug use [5]. There are numerous interventions, such as syringe service program, which are examples of harm reduction. While these specific examples are crucial interventions, it is important to recognize that harm reduction is more broadly any program, policy, or method which focuses on reducing the negative consequences of drug use. Harm reduction is a philosophy and an approach to patients which acknowledges that people who continue to use alcohol, tobacco, or drugs deserve the best medical care we can offer with respect and without judgment.

There are several core principles of harm reduction. Harm reduction is based on pragmatism and recognizes that some percentage of the population will continue to use drugs for a variety of reasons but that some ways of using are riskier than others. While the immediate focus is on reducing harm, this approach does not rule out a long-term goal of recovery. The goals of harm reduction must be viewed as complementary to the goals of treatment. This type of approach respects and values the rights and inputs of people who use drugs and emphasizes self-determination and engagement. Individuals are offered a range of options in a manner that is nonjudgmental and noncoercive. The focus of harm reduction interventions is on the quality of the individual's life and community quality of life. This approach recognizes that people who use drugs benefit from a variety of approaches; therefore, autonomy and having ready access to a range of interventions are necessary to help keep people alive and safe while promoting health. Lastly, this approach celebrates every positive change. Like the popular saying, "don't let perfect be the enemy of the good," this means acknowledging and supporting an individual's most pressing needs and the immediate goal of safety. This philosophy is based on the importance of these incremental gains achieved over time [6].

Unfortunately, and unnecessarily, harm reduction has sometimes been portrayed as contradictory to the goals of treatment and recovery. This is untrue and creates a false dichotomy. In fact, a desire for treatment and recovery often begins through engagement with a caring and nonjudgmental provider around improving health. In addition, many people who use drugs do want treatment but are unable to find accessible, effective, nondiscriminatory treatment programs locally and "are de facto condemned to remain in a condition of dependence and to perpetuate their dependence in social exclusion" [7]. Untreated people who use drugs are thus left in isolation without contact or access to healthcare or social support, which increases the risk to those individuals and to the community more broadly.

A harm reduction philosophy is simply a recognition that human rights, including the right to health and care delivered with dignity and compassion, apply to everyone and should not exclude people who continue to use drugs [5]. What this means practically is that a patient who develops endocarditis from injection heroin use deserves the same degree of compassionate care and good medical treatment as a patient who has a myocardial infarction from untreated hyperlipidemia and obesity. Both are suffering medical consequences from complex chronic medical conditions. We would not refuse to take the latter patient for revascularization even if he had decided not to take his cholesterol medication, so why should it be acceptable to deny a cardiac valve repair to the patient with opioid use disorder?

While this approach with drug use may sound radical, it is actually very similar to the core tenets of patient-centered care. The Institute of Medicine defines patient-centered care as care that is "respectful of and responsive to individual patient preferences, needs, and values and ensuring that patients guide all clinical decisions" [8]. These principles mirror many of the key aspects of a harm reduction approach. In addition to similarities with patient-centered care we use for other medical conditions, this type of approach is also congruent with two core principles of medical ethics, our commitment to non-maleficence and to supporting patient autonomy. A harm reduction approach is also crucial because addiction is a chronic relapsing medical disease. The chronic nature of this illness means that even people currently in remission have a high potential for recurrence of active drug use. This makes the concrete tools of harm reduction, including overdose prevention education and safer use techniques, important for people in remission as well as for people who are actively using drugs to minimize the risk of serious or even fatal negative consequences if a recurrence were to occur.

Not all individuals have a near-term goal of engaging in treatment or recovery; however for those who do, the path can be long and is not always linear. Harm reduction allows providers to do everything we can to prevent negative consequences along that journey. Utilizing a harm reduction approach also recognizes that every encounter with a person who uses drugs is an opportunity for movement and positive change. "If our goal is to promote health and reclaim lives, then we must understand the sometimes circuitous paths through which individuals achieve and sustain such health. We must meet each individual with fresh eyes in every encounter with a belief that each encounter is an opportunity for movement, no matter how small, towards health and wholeness" [9]. Harm reduction also opposes the idea of "hitting bottom" as necessary to motivate individuals to seek treatment. Waiting for further negative consequences to happen to an individual often results in "prolonged disability or death," therefore harm reduction recognizes that "hope and growing aspirations for a better life can be a catalyst to recovery as much as a desire to escape addiction-related pain" [9].

A Review of the Evidence

In addition to being philosophically congruent with a patient-centered care approach, harm reduction interventions are also evidence based. Many harm reduction interventions gained support during the onset of the HIV/AIDS epidemic and have subsequently been rigorously evaluated.

Syringe Service Programs

Syringe service programs provide syringe and injection equipment access, disposal, and/or exchange to people who use drugs, while also offering referral and linkage to HIV and viral hepatitis prevention services, addiction treatment, and medical and

mental healthcare [10]. Syringe service programs have been studied extensively to examine the impact on transmission of HIV and hepatitis C as well as injecting risk behavior. An overview of 13 systematic reviews with 133 studies published between 1989 and 2012 demonstrated the effectiveness of syringe service programs in reducing both HIV transmission and injecting risk behavior among people who inject drugs [11]. This review also demonstrated effectiveness in reducing hepatitis C infection, although the evidence was stronger for syringe service programs combined with access to opioid agonist therapy and other harm reduction interventions [11]. Despite concerns that syringe service programs could increase or encourage drug use, research has not supported these fears. One study of 240 clients at a syringe service program found a decrease in self-reported heroin and cocaine use over time [12]. Another study looked at people who had injected drugs and found that those who had formerly used syringe service programs were significantly more likely to report a substantial reduction in injection, to stop injecting, and to remain in addiction treatment. In addition, people who were newly using syringe service programs were five times more likely to enter treatment [13].

Supervised Injection/Consumption Facilities

Supervised injection or consumption facilities are another well-studied harm reduction intervention. Supervised consumption facilities are medically supervised sites where individuals who use drugs can bring in pre-purchased drugs to use onsite. There are approximately 100 facilities in 66 cities in 9 countries worldwide. A meta-analysis of 75 studies of supervised injection facilities found that they are effective at engaging the most marginalized people who use drugs, promoting safer use, increasing primary care access, and reducing overdose frequency, public injecting, and discarded syringes [14]. An evaluation of the first supervised injection facility in North America similarly found that following the opening of the site in Vancouver there was a decrease in the number of people injecting in public, publicly discarded syringes, and injection-related litter [15]. During the first 4 years that the Vancouver site was in operation, there were 766,486 injections in the facility, resulting in 1004 overdose events in the facility; however there were zero deaths [16]. Based on conservative estimates, this analysis demonstrated that between 2 and 12 deaths would be averted annually with the establishment of one facility [16]. A population-based study also found that the area surrounding the Vancouver supervised injection facility had a 35% reduction in fatal overdoses compared to a 9% decrease in other areas not proximate to the facility [17]. A cost-benefit analysis evaluated the financial implications of establishing a supervised injection facility in Baltimore, Maryland, based on the existing data on cost-effectiveness and reductions in overdose and infectious disease transmission. The study predicted that one facility would cost $1.8 million to establish but would result in $7.8 million in savings by preventing 3.7 HIV infections, 21 hepatitis C infections, 374 days in the hospital for skin and soft tissue infection, 5.9 overdose deaths, 108 overdose-related ambulance calls, 78 emergency room visits, and 27 hospitalizations, while engaging

121 additional people into addiction treatment [18]. In addition to saving costs and reducing mortality, supervised injection facilities may also serve as a portal into treatment. A study following two prospective cohorts of people who use drugs in Vancouver found that 11% engaged in addiction treatment services that are co-located on site at the facility over a 2-year period [19].

Overdose Education and Naloxone Distribution

Overdose education and naloxone distribution programs are another harm reduction intervention which has been shown to save lives and to be cost-effective. Witnessing overdose is common among people who use opioids. A longitudinal study of people participating in an overdose prevention training program found that 36% witnessed at least 1 overdose in 12 months following the training and, of the 312 overdoses that were witnessed, naloxone was administered in 77% [20]. Since 1994, there has been an expansion of community-based programs providing overdose education and naloxone distribution to laypeople. Between 1996 and 2014, a survey of known organizations estimated that naloxone kits were distributed to 152,283 people, and there were documented reports of 26,463 overdose reversals across the United States [21]. An interrupted time series analysis examining the impact of community-based naloxone distribution across Massachusetts which trained 2,912 laypersons found that communities with higher enrollments in the training had the greatest decrease in fatal overdose compared to communities with low enrollment or no enrollment [22]. Overdose education training and naloxone distribution to people actively using heroin has also been shown to be cost-effective [23]. Similar to other harm reduction interventions, a concern frequently raised about naloxone distribution programs is that they may encourage risk taking or increased use. Existing evidence does not support this and a study of 325 participants in a naloxone distribution program found no significant change in self-reported heroin use, with 38% reporting a decrease in use, 35% reporting an increase, and 27% reporting no change [24].

Low-Threshold Opioid Agonist Treatment

Low-threshold opioid agonist maintenance treatment models offer another way to engage especially marginalized populations in treatment using a harm reduction framework. Despite the existence of effective treatment with buprenorphine and methadone, those at highest risk often do not access treatment. Low-threshold treatment models are focused on engaging marginalized patient populations, such as individuals with a high risk of blood-borne disease transmission and overdose, those with a lower socioeconomic level or experiencing homelessness, a history of incarceration, and a high prevalence of co-occurring psychiatric illness. These models are crucial to engage difficult to reach patients and to reduce mortality, particularly given the strength of the evidence showing improved survival among people

treated with opioid agonist therapy [25, 26]. Over the course of the life-span of individuals with opioid use disorder, the probability of not dying before long-term cessation is impacted significantly by exposure to opioid agonist treatment even when treatment is not continuous. A study which followed 794 people who injected heroin between 1980 and 2007 found that 228 died during the observation; however each year of exposure to opioid agonist therapy was associated with a 13% decrease in the risk of death [27]. A large meta-analysis of 122,885 individuals treated with methadone and 15,831 treated with buprenorphine examined mortality rates among individuals in versus out of treatment. This study found that overdose mortality decreased from 12.7 to 2.6 per 1000 person-years for those in methadone treatment versus out and from 4.6 to 1.4 for those in versus out of buprenorphine treatment [25]. Despite the strength of these findings, access to treatment is inadequate and even where access exists treatment models may not be welcoming to all individuals who use opioids. Lack of access to treatment has potentially fatal outcomes. A study of those on a wait list for methadone treatment found that they had a more than ten times increased mortality rate compared to those who started treatment [28].

Support for lower-threshold medication treatment models can be gleaned from studies of interim methadone or buprenorphine treatment, where instead of sitting on a waiting list, individuals are given medication without the additional support of counseling. A study of interim methadone treatment randomized 319 individuals with active heroin use to either interim methadone maintenance for up to 120 days or referral to a community-based methadone treatment programs. Among participants assigned to interim methadone treatment, 75.9% entered into comprehensive methadone treatment at 120 days compared to 20.8% assigned to a waiting list [29]. In addition, the group that received interim methadone had significantly fewer days of heroin use in the past month (4.2 days vs. 26.4 days), and a decrease in opioid-positive toxicology, money spent on drugs, and illegal activity. A more recent study looked at the impact of interim buprenorphine treatment compared to waitlist controls. Among patients randomized to interim buprenorphine, opioid abstinence by toxicology was significantly higher than for those in the control group at 4 weeks (88% vs. 0%), 8 weeks (84% vs. 0%), and 12 weeks (68% vs. 0%) [30]. In addition, individuals who received interim buprenorphine had less frequent injection drug use. Adherence to buprenorphine was incredibly high at 99% and patients rated treatment with high satisfaction scores.

Examples of low-threshold opioid agonist treatment models include programs that offer but do not require counseling, mobile treatment models, and models that offer medication treatment within a syringe service program. Data from a low-threshold clinic in New York which offers buprenorphine without mandated counseling and with less frequent visit requirements found that, among 477 patients treated, the median treatment retention was 57 weeks and overall 60% of toxicology tests were opioid-free [31]. A program which offers buprenorphine treatment within a syringe service program evaluated outcomes among 124 patients and found retention rates at 3, 6, 9, and 12 months of 77%, 65%, 59%, and 56%, respectively [32]. In addition, rates of buprenorphine-positive toxicology were high, with 95% testing positive at 12 months and only 16% testing positive for other opioids.

Mobile treatment models have also been explored as a way of engaging higher-risk individuals who may be less likely to access treatment. A mobile van methadone treatment model was studied in comparison to traditional fixed site dosing and found that mobile treatment engaged a group of patients who were more marginalized, disconnected from treatment, and with more severe illness. Mobile clinic patients were more likely to be African American, homeless, uninsured, using by injection, using daily, have co-occurring psychiatric illness, and have not accessed treatment previously [33]. Taken together, these findings indicate that low-threshold treatment models offer an opportunity for engaging individuals who have not traditionally been reached by the addiction treatment system. Despite this higher-risk patient population, their models achieve reasonably high rates of treatment retention and abstinence.

Safer Use Education

Safer use education offers people who use drugs concrete teaching about how they can reduce the negative consequences of use, particularly the risk of infectious complications and venous damage associated with injection drug use. Safer injection education is important because of the toll infectious complications take on individuals who inject drugs and the healthcare system. Among people who inject drugs, infectious complications, such as skin and soft tissue infections, are the leading cause of hospitalization and emergency department (ED) visit [34]. Globally injection drug use contributes to HIV and hepatitis B and C infections, and 17.8% of people who inject drugs are living with HIV, 52.3% are hepatitis C virus (HCV) antibody positive, and 9.0% are hepatitis B virus (HBV) surface antigen positive [35]. Education about safer use techniques can be shared with a patient in any care setting by a clinician or by a harm reduction agency, such as a syringe service program. Teaching safer injection techniques is important because many of the types of infectious complications and specific microorganisms are associated with particular injection practices. For example, licking needles prior to injection is associated with oral anaerobe infections, such as *Eikinella*; using tap water as a dissolvent increases the risk of gram-negative infections such as pseudomonas; and using lemon juice to dissolve a basic substance like crack cocaine increases the frequency of candida infections [36–38].

Simple practices such as cleansing the skin prior to injection have been shown to reduce soft tissue infections [39]. Providing education about injection practices is also feasible. An evaluation of a one-week pilot intervention that taught safer injection techniques found that participants reported significant reductions in drug intake and injection-related risk behavior following the intervention [40]. Participants also reported increased planning skills, motivation/self-efficacy, and stigma management strategies. This education can be successfully delivered by peers or by nurses or other clinicians [41, 42].

While injection drug use is associated with the greatest risk of infection, individuals who smoke crack are also at risk. Sharing or using makeshift paraphernalia

is associated with an increased risk of hepatitis C transmission and with oral injury. Education and the distribution of safer crack cocaine use kits have been shown to reduce risk. A study of 31 people who regularly smoked crack cocaine evaluated a program that distributed safer crack use kits and found that kits reduced participants' need to share and to commit crimes to obtain money to buy paraphernalia [43]. In addition, this intervention led to an increased awareness about health and personal and community safety. Access to safer crack use kits has also been shown to reduce the frequency of injection use [44]. These kits generally contain glass stems, rubber mouthpieces, brass screens, lip balm, and chewing gum to reduce the harms associated with smoking crack.

Prescription Heroin Programs

Prescription heroin programs, also called heroin-assisted treatment, offer prescribed diacetylmorphine to individuals who continue to use heroin after being engaged for a period of time in methadone treatment. The first of these programs started in Switzerland in the 1990s. Initial studies in Switzerland, the Netherlands, and Germany demonstrated that heroin prescription programs were safe, feasible, and cost-effective [45, 46]. Subsequent randomized controlled trials have demonstrated that prescription heroin treatment results in greater improvements in physical and mental health and reductions in heroin craving and street heroin use compared to individuals continuing to use heroin despite being engaged in methadone maintenance who were not randomized to prescription heroin [47, 48]. In addition, prescription heroin appears to have a mortality benefit. An analysis of mortality rates of individuals receiving prescription heroin over a seven-year period in Switzerland found that mortality was lower compared to the general rate for Swiss people who use drugs or for people engaged in other types of maintenance treatment [49]. This finding was particularly notable given that prescription heroin is utilized for individuals who are considered refractory to other types of treatment. A 2011 meta-analysis concluded that prescription heroin treatment decreases illicit substance use, criminal activity, incarceration, and possibly mortality, while increasing treatment retention [50]. Based on these findings, the evidence supports making prescription heroin treatment available alongside flexible doses of methadone for individuals with treatment refractory opioid use disorder [50].

Incorporating Harm Reduction into Clinical Practice

The evidence supporting a range of harm reduction interventions is important not just for policymakers but also for practicing clinicians caring for people with opioid use disorder. The general philosophy of harm reduction can and should be incorporated into a patient-centered approach for caring for people who use drugs. Also, components of many of the specific interventions which have been studied in the harm reduction literature can be integrated into clinical practice.

Clinicians providing opioid use disorder treatment should provide overdose education and naloxone prescription to all patients, regardless of whether they are currently using opioids given the risk of relapse and fatal overdose. In addition to ensuring access to naloxone, overdose education can provide guidance around never using alone and doing a test dose to try a small amount of a drug to test the strength. For patients who are actively using opioids, starting a conversation around how the person uses, and for those who are injecting where they get syringes and supplies, is crucial. Discussing these details with a patient presents an opportunity for providing safer use education and facilitating access to sterile supplies, for example, through linkage to a syringe service program. If a patient reports sharing injection equipment, a clinician should consider prescribing pre-exposure prophylaxis (PrEP) medication to reduce the risk of HIV acquisition, as recommended by the Centers for Disease Control and Prevention (CDC) [51].

Harm reduction principles also offer important lessons for how we think about and structure addiction treatment programs. Ensuring immediate access to low-threshold treatment with medications for opioid use disorder is critically important to reduce mortality and engage high-risk and marginalized individuals into care. Practically implementing this approach could include committing to same-day medication initiation, making treatment retention a priority outcome, offering but not requiring additional psychosocial interventions in addition to pharmacotherapy, and not terminating patients from care for ongoing drug use.

While this approach has clear applicability to addiction treatment programs, there are also important lessons for how we deliver general medical care to people who use drugs. A qualitative study of people who use drugs exploring their experiences during hospitalization offered valuable insight into what patient-centered care in a general hospital might look like. Some key themes included how care would be improved if hospitals implemented approaches that recognized and were responsive to the subjective health needs, the experiences, and the drug-related needs of people who use drugs [52]. In contrast, the current abstinence focused approach of many hospitals may increase harm by forcing people who use drugs to do so in secrecy in order to hide their use or to simply not come into care or leave prematurely.

Conclusion

Harm reduction is a philosophy and an approach which focuses on minimizing harm and promoting health, rather than necessarily reducing drug use. A broad range of harm reduction interventions has been studied and found to be successful, including syringe service programs, supervised consumptions sites, naloxone distribution, safer use education, low-threshold treatment models, and prescription heroin programs. Many components of these specific interventions can be incorporated into clinical practice. In addition, the general principles of harm reduction can inform a patient-centered care model both within addiction treatment programs and general medical settings to improve the health of and clinical outcomes for patients.

This approach embraces the notion that people who continue to use drugs deserve equitable and dignified care delivered with respect and without judgment.

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9 The Natural History, Clinical Course, and Long-Term Recovery from Opioid Use Disorders

Elizabeth A. Evans and Yih-Ing Hser

Introduction

The opioid crisis has resulted in extraordinary numbers of accidental injuries, infectious diseases, and premature deaths [1], contributing to a historically unprecedented shortening of American life expectancy [2] and resulting in a national public health emergency [3]. Opioid use disorder (OUD) is largely viewed by health experts as a chronic health condition that is best managed with long-term treatment with medications (e.g., buprenorphine, methadone, and naltrexone) that may be required over the lifetime [4]. Because of social stigma and other factors, however, many patients seek or are referred to treatments for OUD without medications, believing that these are merely "replacing one drug (e.g., heroin) with another (e.g., methadone)." For many individuals with OUD, access to medication-based treatments is difficult, expensive, or simply not possible due to lack of available services. For the minority of individuals in need of treatment for OUD who do commence medication treatment, many prematurely discontinue these medications against medical advice. Patient treatment preferences, social and clinical biases against medications that are either an opioid agonist (methadone) or partial agonist (buprenorphine), unavailability of treatment, and barriers to treatment utilization are among the major reasons why a minority of people with OUD ever use these medications. Of those who do, many do not adhere to treatment long enough to achieve sustained benefits.

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Multi-sector task forces are now taking extraordinary collaborative actions to address the opioid crisis [5]. Efforts are focused on rapidly expanding capacity to treat OUD and engage more people with OUD in medication-based treatment [6–9]. In this context, it is critical that health policies and clinical practice guidelines are informed by empirical evidence regarding the long-term course of OUD. In this chapter, first we present key findings on the natural history and clinical course of OUD, and then we summarize what is known about how people achieve abstinence from opioids and sustain their recovery from OUD. We end by offering a few guiding principles for conceptualizing the concept of OUD recovery.

Natural History of OUD

More than two decades ago, researchers at UCLA developed the life course framework for understanding drug use [10, 11]. Since then, we and others have used this approach to identify long-term patterns of stability and of changes in the use of opioids and other substances in relation to transitions across the life span. This approach recognizes how opioid use and other substance use are shaped by time, timing, and temporal processes during an individual's lifetime. It also emphasizes how behavior is influenced by historical and environmental contexts (e.g., the opioid crisis, the HIV crisis, the availability of medications). When we apply this framework to understanding the natural history of opioid use disorder (OUD), we are most interested in mapping the patterns or trajectories of opioid use over time. We also seek to identify how changes in opioid use occur and the extent to which those changes in use are the result of developmental transitions, turning point events, or exposure to addiction treatment and interactions with other health and social services organizations, including the criminal justice system. In this section, we summarize key findings regarding the nature of OUD that emerge when this condition is examined over long periods of time and in relation to broad historical and environmental contexts.

OUD Is a Chronic and Relapsing Condition

Opioid use disorder—addiction—is a chronic disorder typically characterized by recurring cyclic episodes of use, cessation of use, periods of abstinence, relapse to use, and return to addiction and dysfunction [12]. Data from the authors' 33-year follow-up study of people with heroin addiction have shown that heroin addiction is characterized by long periods of regular use and tends to persist over the life course [13] (Fig. 9.1). The study identified predictors of long-term stable recovery among a sample ($N = 242$) of people with heroin addiction tracked and interviewed for up to 33 years. Comparing those in recovery against those not in recovery (people actively using opioids) showed no group differences in pre-addiction deviant behaviors or family problems or school problems. Notably, repeated efforts to cease opioid use had been attempted by both groups by

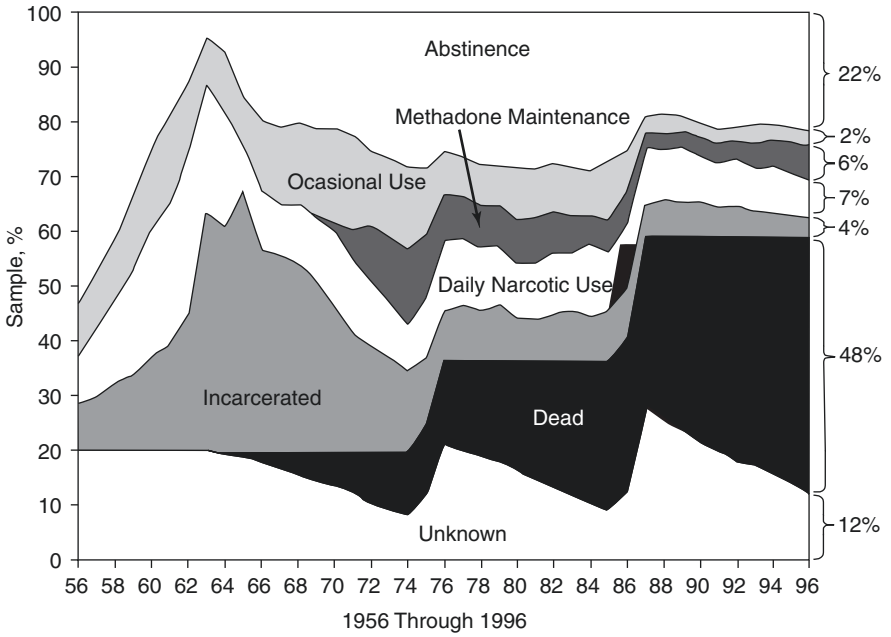

Fig. 9.1 The natural history of narcotics addiction among a male sample. (From Hser et al. [13]. Reprinted with permission from American Medical Association.)

engaging in treatment programs as well as participating in self-help/mutual support groups. Differences were noted in several areas: those continuing opioid use were more likely to be in relationships with people who used drugs, they tended to use drugs to deal with stress, and they had limited social support. Continued use was associated with minority ethnicity, lower self-efficacy, and more psychological distress. Thus, these data suggest interventions might include efforts to increase or capitalize on self-efficacy and to address psychological problems in support of sustaining recovery.

In another work, we synthesized results from 28 studies on the long-term course of opioid addiction, with assessments spanning 10–33 years [12] (Fig. 9.2). A critical finding is that OUD is a chronic disorder with frequent relapses after periods of abstinence attained during formal treatment but difficult for most patients to sustain after treatment ends, regardless of modality.

The studies were selected for review because they had sufficient years of observation (i.e., at least 3 years of observation from baseline to follow-up) and other key parameters (e.g., measures of mortality and abstinence) that are needed to characterize opioid use trajectories. Also, it is important to recognize that most long-term trackings of people with OUD involve cohorts that were established decades ago, have been conducted in the United States and Europe, and are based on people with a heroin-specific OUD recruited from clinical settings (mostly methadone maintenance treatment), and many of whom are criminal justice referrals. The natural

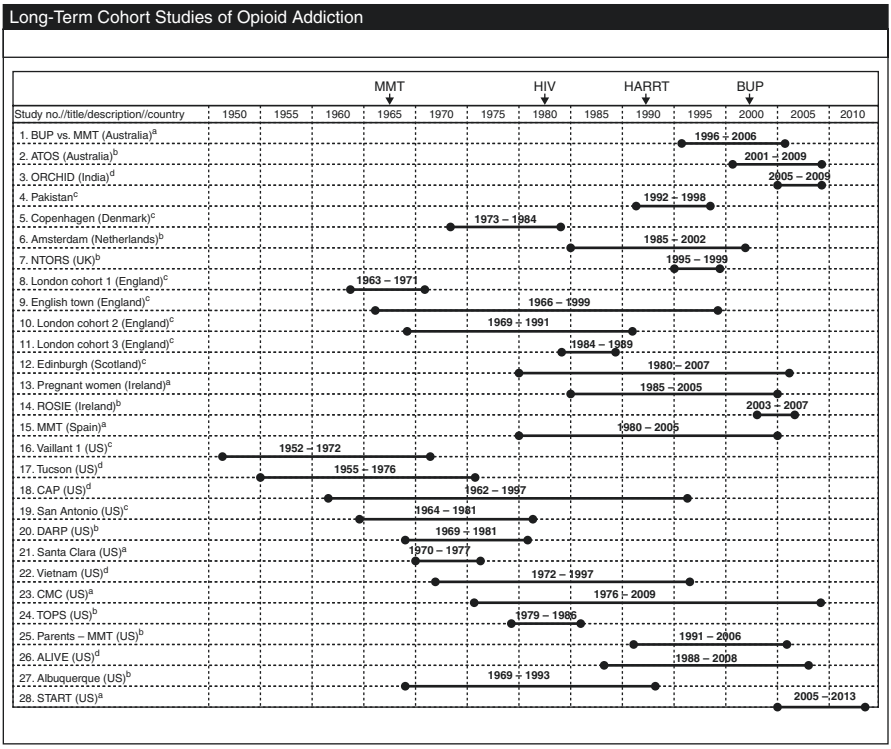

Fig. 9.2 Long-term cohort studies of opioid addiction. (From Hser et al. [12]. Reprinted with permission from Wolters Kluwer Health, Inc.)

history, clinical course, and experiences of recovery among individuals treated more recently or among those with prescription opioid use disorder may be different from those with heroin use disorder. Clearly there is a need for more longitudinal cohort studies of individuals with OUD that reflect the most current contexts such as changing populations and global impacts, treatment options, social policies, and substance types (e.g., prescription opioid medications, fentanyl). Nevertheless, the cumulative results from these long-term cohort studies provide valuable evidence that cannot be obtained using cross-sectional or short-term studies. The preponderance of the evidence generated by these studies also underscores the following two realities that are critical for understanding the long-term course of OUD.

People Do Not "Mature Out" of OUD—They Die Out

The mortality rate of people with OUD is about 6–20 times greater than that of the general population [14, 15]. Furthermore, higher mortality rates are generally observed with longer follow-up periods; with few exceptions, 25–50% of individuals in cohorts that have been followed for 3 or more years are deceased 20 years

after baseline [12]. Neither age nor the chronicity of use predicts recovery from OUD [12]. These findings indicate that people with OUD do not naturally cease opioid use and maintain abstinence as they age—anecdotally deemed a process of "maturing out" of the condition—controlling for all factors; what increases over time is the risk of death [12].

Context Matters as an Influence on OUD-Related Morbidity and Mortality

The mortality rates of people with OUD vary considerably by geographic region and according to other phenomena. For example, the gross average annual mortality rate among individuals with OUD is highest in Asia (3%), followed by Western Europe (2–3%), North America (1–2%), and Australia (less than 1%) [12]. An important factor is whether the cohort under study had initiated opioid use before they encountered the HIV/AIDS era (mid-1980s to early 1990s), when highly active antiretroviral therapy became available. In countries or regions with a high HIV seroprevalence among people who inject drugs, AIDS has been a major cause of death, whereas in low-prevalence countries, overdose, suicide, and trauma played far greater roles [12]. Another factor to consider is whether within a particular country or region, OUD is typically addressed as a criminal justice problem, as has been done historically in the United States, or has been seen as a public health issue, as is more common in much of Europe. Typically, a harm reduction approach that features treatment with comprehensive modalities that include medications (primarily with buprenorphine or methadone) produces better outcomes over the long term than approaches to OUD that emphasize supply control, incarceration for drug-related offenses, and reliance on drug-free modalities such as residential communities and mutual support groups [16]. Findings underscore how individuals' long-term course of OUD may be shaped differentially by variations in local treatment policies, criminal justice policy, and historical contexts.

Clinical Course of OUD

Variations in onset of opioid use and progression over time suggest there are salient factors and experiences that influence whether OUD occurs, worsens, or is amenable to or resistant to treatment. Changes in opioid use occur when individuals are exposed to treatment and as a result of interactions with other health and social service systems and as a result of developmental transitions and other critical life events.

Treatment of OUD with Medications Is a Critical Life Event

When used appropriately, methadone and buprenorphine are both effective medications for the long-term stabilization of individuals with OUD [17–21]. Specifically,

individuals with OUD who are retained in treatment with medications have lower mortality [14, 22], less opioid use [20, 23], less HIV risk, and other positive outcomes [16, 24]. For many individuals, OUD is a chronic condition that may require life-long treatment with medications.

Despite the beneficial effects of treatment with medications, few people with OUD ever receive any kind of treatment and of those who do enter treatment; it is not unusual for people to use opioids for many years before initiating care [12]. Initiation of treatment in young adulthood rather than in older developmental stages is associated with better outcomes [25, 26], highlighting the benefits of treating problematic opioid use soon after it develops. However, because the beneficial effects of medication treatment (e.g., reduced craving, suppression of potential reinforcing effects of illicit use of opioids) are generally short-lived, many people relapse to use soon after treatment cessation, and subsequent treatment episodes are commonplace. More favorable outcomes are associated with continued engagement with treatment and longer cumulative treatment duration [27, 28]. Unfortunately, many people with OUD spend most of their time out of treatment [29]. Multiple treatment episodes are often needed to help achieve sustained abstinence from opioids [10].

Comparative Effectiveness of Medications to Treat OUD

Several effective medications for treating OUD are available. Methadone is a Schedule II full opioid agonist that has been used in the United States for almost five decades. Methadone is available only in specialized, government-licensed clinics. Recent efforts have focused on developing medications that can be used to treat OUD in medical office settings. The two approved medications available for use in office-based settings are (1) buprenorphine (alone and in combination with naloxone [Suboxone® or generic]), as well as an sustained-release formulation (Sublocade®), which is administered monthly by injection; and (2) naltrexone in an oral formulation and an extended-release formulation (Vivitrol®), which is administered monthly by injection. Buprenorphine is a partial opioid agonist and has a superior safety profile to that of methadone, which produces a ceiling effect that reduces overdose risk and limits reinforcing effects of illicit use of opioids. Naltrexone is a full opioid antagonist that binds to the opioid receptor to eliminate reinforcing effects of opioids regardless of dosage. These two medications and their delivery in office-based settings supervised by clinicians allow access to treatment for the many patients who would not seek or cannot obtain care in methadone programs.

Importantly, most long-term studies on the effectiveness of medications to treat OUD are based on methadone; few such studies have examined buprenorphine, and none have examined the long-term impacts of extended-release naltrexone or other newer medications to treat OUD. When examined in the short term (24 weeks), induction to extended-release naltrexone is more difficult than buprenorphine which, in turn, negatively impacts overall risk of return to opioid use; once initiated,

however, both medications are equally safe and effective [30]. Findings highlight the need to facilitate induction to extended-release naltrexone and improve treatment retention for both medications [30]. Longer-term studies are needed to understand how extended-release naltrexone shapes OUD over the life course.

A critical finding that has emerged from comparisons of the long-term outcomes of buprenorphine and methadone treatment for OUD is that there are few differences in outcomes and treatment with each medication is associated with a significant and clinically meaningful reduction in opioid use unless individuals cease pharmacotherapy [20]. As presented in Fig. 9.3, both buprenorphine and methadone treatments (relative to no treatment) are associated with less opioid use over approximately 5 years, and there is no difference between the two medications in opioid use.

There have been considerable efforts to expand buprenorphine treatment capacity in the United States. This work has focused on needed increases in buprenorphine accessibility, for example, by reducing its price; ensuring Medicaid, Medicare, and other types of health insurance to cover expenses for the medication and its medical management by clinicians; removing barriers such as prior authorization; and training more clinicians to prescribe it. However, simply making buprenorphine treatment more available is not enough. Generally, individuals who access buprenorphine treatment remain engaged in it for less time than those who receive

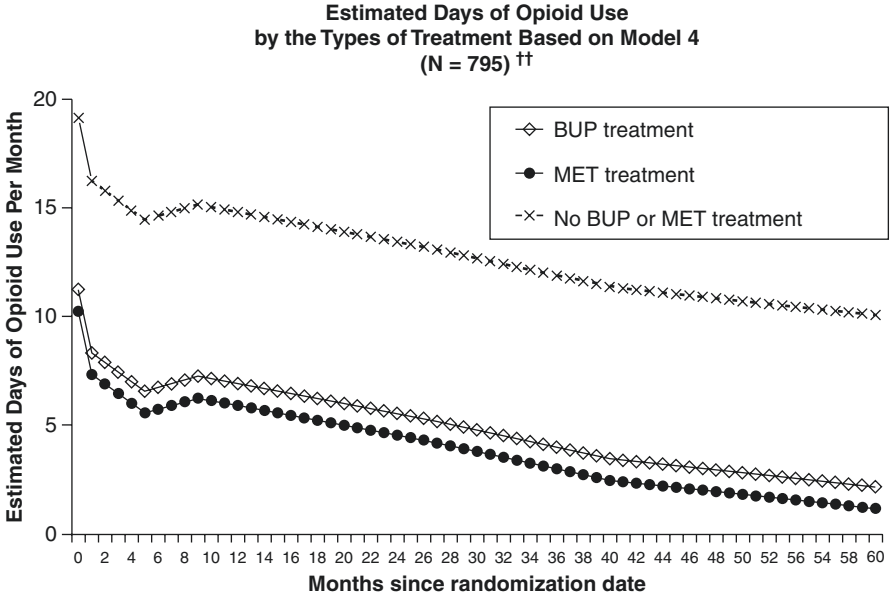

Fig. 9.3 Estimated days of opioid use by the types of treatment. BUP, buprenorphine; MET, methadone. (From Hser et al. [20]. Reprinted with permission from John Wiley & Sons.)

methadone [20, 31, 32]. When examined over 5 years, only 10–20% of individuals treated for OUD remain in buprenorphine treatment [33]. Findings suggest that to increase buprenorphine utilization and retention in treatment, public strategies must support increased treatment capacity and also develop interventions to improve long-term medication adherence.

Other Key Transitions and Turning Points

Other than studies of entry into treatment with medications for OUD, little research has been conducted to investigate the critical events or turning points that are responsible for the major shift from initial use of opioids to development of OUD to treatment and recovery. Some studies, however, provide insights into the social determinants of OUD and the underlying processes.

Personal Experiences and Events Opioid use can change as individuals transition through social roles (e.g., parent, employee) or experience dramatic life events (e.g., loss of a significant family member or relative). Exposure to childhood sexual and physical abuse is more common among people with OUD [34], and experiences of such trauma increase the risk of persistence of opioid and other substance use disorders [35]. Engagement in rewarding nondrug activities (e.g., employment, vocational training) and supportive relationships (e.g., friends, family, spouse) appears to be important for achieving cessation of opioid use or maintenance of abstinence [11, 36].

Physical and Mental Health Continued opioid use is associated with trauma histories (e.g., sexual and physical abuse) [37, 38], comorbid mental health disorders (anxiety, depression) [39–41], and chronic pain [42]. It is difficult to untangle the overlapping risk factors and causes of these diseases and chronic conditions. For example, mental health disorders and chronic pain may precede prescription opioid use and addiction, or these conditions may develop after OUD, either as an expected health condition or as a consequence of OUD. Recent research suggests that most patients with OUD who are treated in general healthcare settings have chronic pain conditions; the majority of these patients have chronic pain before their first OUD diagnosis, and this clinical profile is associated with severe mental health and physical health conditions [43]. Findings regarding these complex physical and mental health conditions point to the need for better models of assessment and coordinated care plans to address OUD.

Incarceration Histories of criminal activity and involvement with the criminal justice system are among the key factors associated with continued heroin use [12]. Experiences of repeated incarceration and criminal justice supervision generally do not reduce relapse to opioid use or help support recovery from OUD. Instead, a return to opioid use after release from incarceration is a common occurrence. Exit from prison is a period of high-risk for mortality, particu-

larly due to fatal opioid overdose, when people return to opioid use but have lost tolerance to their previous levels of use [44, 45]. Furthermore, heroin abstinence episodes are shorter-lived following incarceration than when preceded by sustained treatment [46]. Efforts are underway now to expand capacity to deliver OUD medications within correctional settings. Currently, limited information is available regarding criminally involved participants' utilization of OUD medications while in jail or prison, their subsequent OUD pathways, and the long-term outcomes.

These critical turning points and other factors that shape the course of OUD have particularly strong impacts on vulnerable populations, e.g., rural populations, race/ethnic minority groups, pregnant and parenting women, and justice-involved individuals [4, 12, 47]. Targeted efforts focused on these populations in particular are needed to reduce existing health disparities in OUD and related morbidity and mortality.

Long-Term Recovery from OUD

There is no standard definition of the concept of long-term recovery from OUD. This reality helps to explain why there is wide variation in the outcome measures that are used by studies of people treated for opioid use disorder [48]. Most long-term studies have defined OUD recovery as decreases in use or as having achieved opioid abstinence, thus abstaining from heroin and other opioids for some period of time [12]. Other studies have included dimensions besides abstinence in the definition of OUD recovery, including gainful employment and no arrests or incarcerations [12]. It is in this context that over the past decade, we, along with our collaborators at UCLA and elsewhere, have quantified the extent to which individuals with OUD do achieve lasting opioid abstinence.

Distinctive Trajectories of Opioid Use

In our recent work, we identified distinctive opioid use trajectories among 795 people using opioids after their enrollment in a multisite trial and followed for up to 8 years [49]. Four distinctive patterns of opioid use were identified: low use (42.0%), high use (22.3%), increasing use (17.1%), and decreasing use (18.6%) (Fig. 9.4).

Most notably, groups that exhibited patterns of high use and increasing use had greater severity in problems related to drug use, employment status, legal problems, and social/family relationships, and they had worsened mental health functioning at follow-up. Participation in treatment significantly accounted for differences in opioid use. Results suggest that continued treatment is necessary to reduce risk for opioid use and related adverse consequences, particularly among people who inject opioids or other individuals at risk for consistently high level of

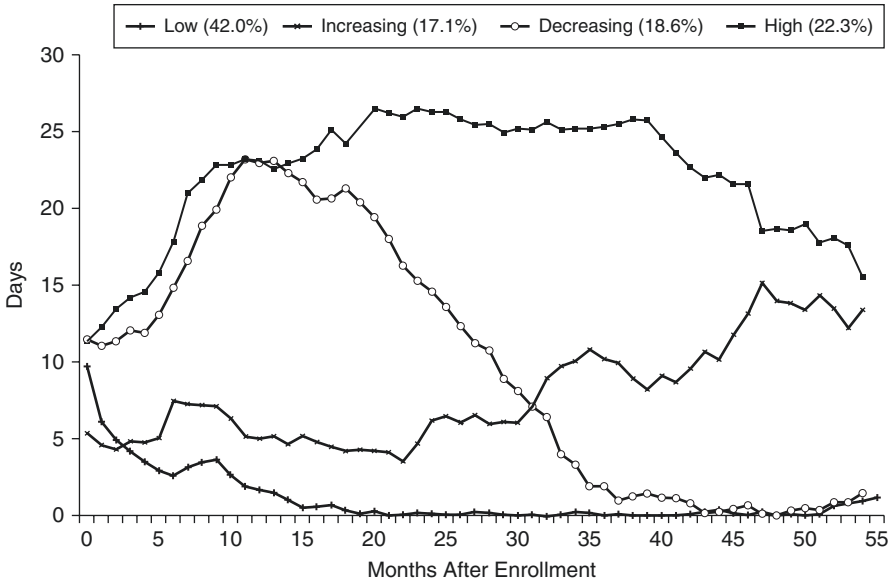

Fig. 9.4 Opioid use trajectories. (From Hser et al. [49]. Reprinted with permission from Wolters Kluwer Health, Inc.)

opioid use. In broader terms, uncovering heterogeneities in longitudinal patterns of opioid use among individuals with OUD can increase our understanding of disease progression and treatment responses to improve care.

Maintenance of Opioid Abstinence

We have also sought to identify whether a particular duration of opioid abstinence is associated with better life course outcomes. This line of research reveals that maintenance of opioid abstinence for 5 years substantially increases the likelihood of future stable cessation [11]. Furthermore, individuals who maintain opioid abstinence for at least 5 years have better life outcomes in several domains (family and social relationships, employment, legal problems, mental health) than those who have been abstinent for fewer years [50]. These findings provide a benchmark for reduced risk and therefore serve as a potential target for developing interventions and managing risks. At the same time, however, it is important to recognize that only about one-third of people with OUD achieve 5 years of opioid abstinence [12, 50]. Also, many people who have achieved opioid abstinence continue or increase their use of alcohol and other substances [11, 51, 52]. This is particularly significant because polysubstance use among people being treated for OUD curtails the beneficial effects of that treatment over time [53]. These phenomena affirm the complexity and chronicity of OUD and underline how challenging it is for individuals to sustain abstinence.

A Life Course-Informed Conceptualization of OUD Recovery

We end this chapter by offering a few guiding principles for using a life course framework to conceptualize the meaning of long-term OUD recovery. Before turning to this topic, however, it is important to recognize that promoting and sustaining recovery from substance use disorders is a key concept in healthcare policy [54, 55], yet what was recognized more than a decade ago—the field lacks consensus on the definition of "recovery" [56]—is still true today. The concept of recovery is rooted in mutual self-help organizations dating to the nineteenth century, which was incorporated into the later model of recovery in the 12-step "disease" model of addiction [57–59]. Over the years, recovery has often been defined as a particular duration of abstinence following an intervention [12]. In their research with people who used heroin, Maddux and Desmond [60] set a criterion of 3 years of abstinence from the primary drug and no abuse of other drugs. Limited empirical evidence documents specific "benchmarks" or a threshold of time that supports recovery as a stable and enduring outcome [61]. Our work and that of others suggest a minimum of 5 years for determining stability of recovery [11, 62].

In contrast to the relatively narrow definition of recovery as total abstinence, other research emphasizes the diverse ways in which the meaning of recovery is construed in the personal narratives of people who use substances, including how self-identity is shaped through social interactions with others [63–65]. In a survey of inner-city residents who had DSM-IV dependence-level use of crack or heroin, most defined recovery as total abstinence, but they also included references to a bountiful "new life," an ongoing process of growth, self-change, and reclaiming the self [66]. An empirically derived definition of recovery based on lived experiences of people with the condition includes the elements of being honest with oneself, handling negative feelings without using substances, being able to enjoy life without drinking or using drugs, and a process of growth and development [67, 68]. Institutions have defined recovery broadly in the past decade as "a voluntarily maintained lifestyle characterized by sobriety, personal health, and citizenship" [69, 70] and "as a process of change through which individuals improve their health and wellness, live self-directed lives, and strive to reach their full potential" [55]. Others have developed the concept of "recovery capital," denoting personal and social recovery resources that have been developed over the course of a life that can be brought to bear on the initiation and maintenance of recovery [71, 72].

We add to this literature on recovery by reflecting on what we have learned from applications of the life course drug use framework. We offer a few guiding principles for conceptualizing the meaning of OUD recovery. First, understanding of OUD as a chronic relapsing condition provides a framework for considering as indicators of positive outcomes both reductions in opioid use and also any period of opioid abstinence. Individuals who make these gains may be on a path toward continuous abstinence and, independent of whether or not they do eventually achieve continuous abstinence, they are likely to incur reduced risks for mortality and morbidity and achieve a better quality of life. Thinking about OUD recovery

in terms of these other indicators, and not defined only as continuous abstinence, represents a conceptual shift that is in need of continued discussion and empirical investigation.

Recovery includes constructs of health and wellness as well as functioning in other life domains. If an individual has reduced or stopped using opioids but continues to suffer from chronic pain and symptoms of mental illness, commit crime, engage in family conflict, and be unemployed, then it would be a rather hollow "recovery" and likely to be short-lived. Furthermore, it may be more sensible to identify recovery in terms of improvements in specific domains. For example, it may be useful to consider "recovery of cognitive functioning" or "recovery of vocational functioning" to signify improvements in specific areas. This approach realistically emphasizes states of relative and partial recovery that individuals can achieve by increments, progressing toward a more holistic recovery.

The precepts of recovery in some circles preclude the use of medications, insisting on total abstinence from all substances of intoxication, including those that are approved medications for treating OUD. The use of medications to treat OUD should not be considered contrary to recovery and is not the same as illicit use of other opioids. Adherence to methadone and buprenorphine medications is often the only way that most people are able to initiate and then maintain recovery.

Recovery is both a process and an achieved status. It can come and go over time. People with a history of substance use disorder typically refer to themselves as being "in recovery" and rarely as having "recovered," signifying that a return to use is possible (and is to be guarded against). Time is clearly needed to determine whether recovery from OUD has been adequately achieved and the individual is in a state of recovery that is durable. In this sense, recovery is by its nature a dynamic concept that takes time to determine.

Finally, recovery does not happen in a vacuum. Instead, genuine recovery occurs when there is the development of a new self who is a non-substance-using individual and who interacts within personal and social environments that support recovery. Furthermore, the ability of people to achieve recovery changes across place and time and as situated within the opportunities and constraints of history and social circumstance. Therefore, recovery is a goal that is governed by a set of interrelated factors at the individual and contextual level, requiring a holistic view of the patient, arrangement of services that are tailored to that patient, and access to resources that constitute recovery-supportive environments.

Conclusion

In many areas of the country, opioid-related morbidity and mortality continue to worsen despite a significant allocation of public resources to solve the problem. In this chapter, we document what is to be gained when opioid use disorder is observed over the life course. When viewed from this perspective, opioid use disorder is understood as a chronic relapsing health condition that is exacerbated by factors such as interactions with the criminal justice system, limited access to

medications to treat opioid use disorder, chronic unemployment and conditions of poverty, physical/psychological trauma and related mental illness, social isolation, and poor social support. Developments in pharmacotherapies to treat opioid use disorder and innovative means of administration have yielded important advances in effective medication-based treatments, yet significant obstacles to their broad diffusion remain. Changes in perceptions about opioid use disorder as a chronic condition and about the effectiveness of pharmacotherapies indicate a public health approach that may slowly supersede the criminal justice approach to addressing this condition. This chapter provides an overview of problems related to opioid use disorder as they have emerged and as they are societally and clinically addressed, emphasizing the management and treatment of opioid use disorder with effective use of available pharmacotherapies and within environments that are supportive of recovery.

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Enhancing Treatment Access and Effectiveness: Toward Patient-Centered Models of Care

10

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Abbreviations

HCV	Hepatitis C virus (HCV)
HIV	Human immunodeficiency virus
LGBTQ	Lesbian, gay, bisexual, transgender, queer
MMT	Methadone maintenance treatment
NSDUH	National Survey on Drug Use and Health
OTP	Opioid treatment program
OUD	Opioid use disorder
SUD	Substance use disorder
US	United States

Introduction

In the United States (US), despite the availability of safe and effective pharmacotherapy and psychosocial treatments for opioid use disorder (OUD), a minority of people who need treatment receive it [1]. As opioid use, OUD and overdose have skyrocketed over

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the past two decades, the need for treatment has increased; however, the fragmented system of substance use disorder (SUD) treatment only reaches a small proportion of those in need [2, 3]. Annually between 2004 and 2013, fewer than 20% of those in need of OUD treatment received treatment without significant increase over that period [4]. Despite increasing availability of pharmacotherapies, including buprenorphine and naltrexone, in general medical settings, OUD treatment use has not kept up with increasing diagnoses of OUD [5]. Engaging more people in OUD treatment will require OUD treatment models that are available, accessible, and acceptable to people with OUD.

Problems stemming from OUD have affected much of the United States. There are approximately 2.5 million people in the United States with OUD according to the National Survey on Drug Use and Health (NSDUH) [6]. In 2015, the latest year available, an estimated 91.8 million adults (37.8% of the total population) used a prescription opioid, 11.5 million adults (4.7%) misused them, and 1.9 million adults (0.9%) likely had prescription OUD [7]. Additionally, approximately 0.8 million adults (0.3%) used heroin and 591,000 (0.2%) likely had heroin use disorder, but these numbers may be undercounts [6, 8]. Between 1980 and 2014, mortality from drug use disorders increased in every county in the United States – mostly driven by deaths involving opioids [9]. In 2016, there were 42,000 opioid-related drug overdose deaths – a five-fold increase in comparison to 1999 [3]. Infections associated with OUD, such as human immunodeficiency virus (HIV), hepatitis C virus (HCV), endocarditis, and soft tissue infections, are also increasing [10, 11]. Data describing the entire population of people with OUD are lacking; however, there is likely broad sociodemographic variability with many different communities and individuals affected by the "opioid epidemic." Thus, the full spectrum OUD treatments must be readily available in every community and flexible enough to meet the needs of a diverse population.

In 2017, the US Surgeon General recommended a comprehensive strategy to reduce overdose deaths, which included expanding access to OUD treatment [12]. In the United States, there are three FDA-approved medications for OUD treatment (buprenorphine, methadone, and naltrexone) and several evidence-based psychosocial or behavioral treatments available in outpatient or residential settings [12]. International and US data suggest that mortality is reduced by half or more among people receiving opioid agonist treatments (buprenorphine and methadone) [13, 14]. Naltrexone is an opioid antagonist, and clinical trials of a long-acting injectable formulation are promising with people reducing illicit opioid use while they remain in treatment [15, 16]. Observational data demonstrate that residential treatments, including those using 12-step or therapeutic community approaches, are also effective given sufficient length of treatment [17]. Additionally, other psychosocial or behavioral treatments, such as contingency management (i.e., payment through vouchers for achieving milestones in behavior change) or family therapies, also have evidence of effectiveness in a range of SUDs [17, 18]. Preventing OUD-related deaths will require other strategies, such as increasing naloxone access, improving pain management, and expanding supports for high-risk groups (e.g., people leaving jail or prison), but improving treatment access is feasible and likely to be high-yield. True accessibility will require treatments that are available, affordable, and acceptable to people with OUD.

While making OUD treatment more accessible will benefit the many people who want but do not receive treatment, many people with OUD do not seek out treatment on their own. Factors such as stigma, distrust of the health-care system, and misconceptions about treatment may make current OUD treatment approaches unacceptable to many people. Pressure from friends and family, or coercion from employers or the criminal justice system, can increase uptake of OUD treatment; however, improving the acceptability of treatment could also increase treatment use [19]. There may be therapeutic roles for coercion, meaning leveraging consequences such as legal sanctions or job loss to encourage treatment uptake, but there are also ethical limitations to this approach [19, 20]. Available evidence does not support use of compulsory SUD treatment, where people are forced into treatment without choice, which can lead to human rights violations and other harms [21]. Even among people who initiate OUD treatment, many drop out of treatment early, which suggests suboptimal engagement in the treatment. Efficacious treatments will have no impact if people remain out of treatment. In order to increase engagement in OUD treatment, treatments must be delivered in patient-centered ways that are acceptable to people with OUD.

This chapter will focus on describing patient-centered approaches to OUD treatment. Patient-centered care emphasizes that patients' individual needs should be at the center of treatment decisions, and patients should be active participants in their own care, where their wishes are elicited, respected, and honored to the extent that they improve health [22]. We conceptualize patient-centered OUD care as differing from OUD treatment. If OUD treatment solely focuses on goals of abstinence from illicit opioid use, we believe that patient-centered OUD care should allow patients to set their own goals of care, and address broad health and social needs, thereby improving care engagement regardless of commitment to abstinence or reducing opioid use.

Each section in the chapter will present ways to improve the availability, accessibility, and acceptability of OUD treatment and care. The objectives are (1) to describe barriers to OUD treatment; (2) to present patient preferences for OUD treatment; (3) to recommend modifications to current *OUD treatment* models in the United States that would make treatment more available, accessible, and acceptable to people with OUD; and (4) to present a patient-centered model of *OUD care* that focuses on engagement, retention in care, and harm reduction while serving both people who plan to stop using illicit opioids and those who do not (Table 10.1).

Table 10.1 Key definitions for patient-centered opioid use disorder treatment

Availability	Availability means that people with OUD are able to receive their choice of OUD treatment (methadone, buprenorphine, naltrexone, intensive outpatient treatment, or residential treatment) within their own community
Accessibility	Accessibility means that OUD treatments are available in a timely manner, affordable, and without burdensome health insurance restrictions or programmatic requirements
Acceptability	Acceptability means that OUD treatments are delivered in ways that respect and honor patients' goals and preferences for treatment

OUD opioid use disorder

Barriers to Treatment

Maximizing OUD treatment uptake will require a system where treatment is available, accessible, and acceptable, and also perceived as valuable and desirable to the user. Many communities lack availability of methadone maintenance treatment programs, only 3% of US primary care physicians are certified to treat OUD with buprenorphine, long-acting naltrexone costs more than $4000 dollars for a 24-week course of treatment, and nearly half of nonprofit substance use disorder treatment facilities have no contracts with managed care plans [23–26]. People cannot use OUD treatment if it is unavailable and unaffordable. A full discussion of the economic barriers to OUD treatment is beyond the scope of this chapter, but others have recently reviewed mental health parity laws, expansion of health insurance coverage through the Affordable Care Act, and other potential solutions to rationalize how treatment is paid for in the United States [25, 27]. This section will briefly present data about access to OUD treatment, and then will shift to acceptability of OUD treatment, demonstrating how ambivalence, stigma, and "high-threshold" treatment requirements may limit interest in and acceptability of OUD treatment.

Many people with OUD do not perceive a need for treatment and therefore do not seek care. Data from the 2016 NSDUH suggest that only 6% of the 6 million adults who could benefit from SUD treatment actually consider themselves to need treatment (data specific to OUD has not been published) [28]. Respondents may have had negative impressions about treatment, and like any consumer-driven industry, making treatment more desirable should increase utilization; however, there are other barriers to treatment. Among those who did perceive a need for SUD treatment, but did not receive it, the most common reasons were that they were not ready to stop using the substance, had no health insurance coverage, did not know where to go for treatment, could not find the treatment they desired in their community, seeking treatment might cause their neighbors to have a negative opinion about them, or it might affect their work [28]. These answers reflect a few common themes: access, ambivalence, and stigma.

Treatment Access

Reasonable access to OUD treatment is limited by availability, waiting lists, costs, lack of insurance coverage, and restrictions placed on individuals by the criminal justice system. In the United States, methadone maintenance treatment (MMT) is only offered in federally licensed, highly regulated opioid treatment programs (OTPs). When a person with OUD starts MMT, they typically must attend the program at least 6 days a week, nurses administer daily methadone doses, psychosocial counseling is mandated, and the right to take home medication is earned with continual abstinence. In 2016, there were 1300 OTPs in the United States with 345,000 patients who received MMT, but treatment is unavailable in large parts of the country [29]. With the goal of expanding access to OUD treatment outside of OTPs, the Drug Addiction Treatment Act of 2000 allowed for office-based prescribing of

buprenorphine maintenance treatment with fewer regulations. However, prescribers must acquire a waiver from the Drug Enforcement Agency, which requires an additional 8 hours of training for physicians and 24 hours of training for physicians assistants and nurse practitioners. Certified prescribers also must be able to refer for psychosocial counseling, monitor for diversion of medications, and have limits on the number of buprenorphine patients under their care at any one time [30].

Access to opioid agonist treatments (buprenorphine and methadone) is clearly limited. In 2012, only 47% of counties in the United States had a physician who was certified to prescribe buprenorphine [23]. An estimated 30 million people or 10% of the population lived in counties, which were mostly rural, lacking a buprenorphine-certified physician [23]. In 2011, in Washington State, 28% of the population lacked an MMT program and 7% lacked either a MMT program or buprenorphine-certified prescriber in their county [24]. More recent estimates suggest that nationally only half of community health centers, which are located in medically underserved areas of the United States and care for a low-income population, prescribe medications for OUD [31]. Additionally, people with OUD who are referred for treatment through the criminal justice system rarely receive methadone or buprenorphine. In one study, including more than 70,000 people receiving OUD treatment, nearly 25% of the sample had been referred by the criminal justice system, and only 4.6% of these people with OUD received agonist medications, while 40.9% of people referred from other sources received agonist medications [32].

Access to psychosocial or behavioral OUD treatments is also limited. The majority of substance use disorder treatment is publically funded, but only 60% of US counties had substance use disorder treatment facilities that accepted Medicaid insurance in 2009 [33, 34]. If substance use disorder treatment programs in urban areas can serve a 15 mile catchment area, then individual states had a range of underserved urban areas from 0% in New Jersey or Rhode Island to 34% in Arkansas [35]. Even when treatment facilities are available, diffusion of evidence-based practices to substance use disorder treatment programs has been slow [36].

Ambivalence

Even with improved access to OUD treatment, a large proportion of people with OUD will not seek out treatment. Ambivalence is common with addiction, meaning that people simultaneously hold positive and negative feelings about their substance use [19]. Changes to neuroanatomy and functioning that accompany addiction affect executive function, including self-regulation, decision making, and assignment of relative values [37]. Within the prefrontal cortex, impaired neurotransmitter signaling may affect one's ability to resist urges to use intoxicants or follow through on decisions to enter treatment [37]. However, even if people are not ready or able to enter OUD treatment that focuses on abstinence from opioids, a model of OUD care emphasizing engagement, harm reduction, and prevention may be more acceptable. A later section in this chapter discusses the potential differences between "care" and "treatment" for OUD. An important objective in improving OUD

treatment access is keeping people engaged in care when they express ambivalence about stopping opioid use, so that they can benefit from other health services and easily start treatment if they become ready.

Prochaska and DiClemente proposed the Transtheoretical Model to explain how people change behaviors, including those related to addiction [38]. Their hypothesized "stages of change" include the following: (1) precontemplation, when there is no intention to change in the near future; (2) contemplation, when people recognize that a problem exists and are thinking about changing it; (3) preparation, when people have committed to change; (4) action, when people modify their actions, experiences, or environment to support change; (5) maintenance, when people work to prevent relapse and consolidate gains from the changes; and (6) relapse, when people revert back to the initial behavior [38]. This model focuses on internal or psychological factors that are located within an individual, such as motivation or readiness to change, while others have suggested that external or structural factors, such as social relationships, economic factors, or treatment availability, are also critical for addiction treatment uptake [39]. Nonetheless, the "stages of change" construct is useful, because standard models of OUD treatment in the United States, in which entering treatment typically requires considerable effort, expense, and a commitment to abstinence, create a high threshold for action. These "high-threshold" OUD treatment models are unlikely to reach people who are precontemplative or contemplative about changing opioid use. Reducing the harms of illicit opioid use, for example, by using sterile syringes for injection drug use instead of sharing syringes, may be a more acceptable goal for someone precontemplative about stopping opioids (see Chap. 8). However, harm reduction goals often conflict with medical models of treatment [40]. Thus, a truly patient-centered model of OUD care would be able to meet the needs of people with OUD regardless of their stage of change.

There are ways to help people with OUD explore ambivalence about treatment. Education about OUD treatments can be directed at common myths or misunderstandings about pharmacologic and behavioral treatments [41, 42]. Peer recovery specialists and OUD treatment providers can collaboratively outreach to and engage people with OUD in care (see Chap. 7) [42]. Motivational enhancement therapies can be delivered in a variety of settings (e.g., syringe service program) that serve people with OUD [43]. However, motivational enhancement therapies may not increase treatment uptake without also addressing structural barriers to care [43, 44]. Even if exploring ambivalence about opioid use does not promote treatment uptake, people with OUD can be linked to other needed mental health or social services. Ultimately, though, if OUD treatment is perceived as ineffective, overly controlling, or otherwise onerous, then more acceptable and patient-centered options will be necessary to optimize treatment use.

Stigma

Stigma regarding OUD is another key barrier to treatment. Opioid agonist treatments are stigmatized as well. Stigma can be defined as "a socially conferred mark that distinguishes individuals who bear this mark from others and portrays them as

deviating from normality and meriting devaluation" [45]. Ambivalence about substance use may be influenced by stigma, because seeking care for a SUD would mean taking on the stigmatized mark and could result in social devaluation, discrimination, and negative mental health consequences. For example, people may fear that receiving SUD treatment could lead to discrimination when seeking future medical care or affect employment opportunities [46–48]. Instead of engaging in OUD treatment, people may choose to keep their substance use private [47].

Health-care providers often hold negative views of people with substance use disorders, which can affect the care that they provide, including a lack of empathy [49, 50]. This occurs in hospitals, pharmacies, and general healthcare settings, but even OUD treatment providers may also hold stigmatized views of people with OUD [48, 51]. Fear of discrimination may prevent people from seeking health care except in emergencies. Additionally, people who have negative experiences with OUD treatment may be less willing to seek care in the future [52, 53].

Opioid agonist treatments are also highly stigmatized [54]. One qualitative study of people who inject drugs reported that participants saw MMT as more highly stigmatized than injecting drugs, which prevented them from entering treatment [48]. Starting agonist medications, which leads to physical dependence, may be seen as a step backward in recovery [55]. Within society at large, communities have protested or driven out MMT programs [56]. Government officials continue to criticize agonist medications as simply, "substituting one opioid for another" [57]. Within the recovery community, people taking agonist medications may experience stigma while attending 12-step meetings [56]. These factors likely affect acceptability of OUD treatment.

Decreasing stigma will require broad efforts in society and in health-care settings [56]. Community organizations, such as the Drug Policy Alliance, are working to promote public policies that reduce stigma. Communicating positive stories about addiction is effective in reducing stigma [58]. Person-first language, such as people with OUD, is preferable to stigmatizing language, such as "addict" or "junkie," because it has been associated with more positive attitudes, even among health care workers [59]. Mental health and SUD parity laws can ensure that health insurance coverage includes evidence-based SUD treatments. Finally, reducing reliance on the criminal justice system to solve OUD-related problems would shift focus to treating OUD as a health condition instead of a moral failing. Portugal decriminalized illicit substance use, which was followed by reductions in substance use-related harms [60].

"High-Threshold" Models of Care

Improving the acceptability of treatment will also require alternative options to the standard OUD treatment models in the United States. While effective, OUD treatment is primarily offered in "high-threshold" settings, where patients must comply with strict rules, undergo frequent urine drug testing, and ongoing substance use can result in program discharge. Opioid agonist treatments often require daily program attendance. Residential treatments, such as therapeutic communities, typically

require lengths of treatment that are greater than a year [61]. High-intensity programs offer structure and support for people with high needs (e.g., comorbid psychiatric illness), but they also create a high threshold of motivation for people to engage in care.

Opioid agonist treatments are closely monitored and regulated, because these medications can be diverted (i.e., sold, traded, or given) to people who are not in treatment, which could harm public health. However, retention in these standard high-threshold models of OUD treatment is suboptimal with only 50–60% of people who initiate treatment with methadone or buprenorphine continuing treatment for at least a year [62, 63]. People drop out treatment for many reasons, but requiring frequent visits for monitoring and medication pick-up are a common source of frustration among patients of each treatment modality [64–66]. People with OUD also commonly use other illicit substances, but they may be discharged from treatment due to ongoing substance use [66]. If people are unable to follow strict program rules, there usually are no low threshold models of OUD treatment or care, where they can still receive agonist medications.

For residential and outpatient SUD treatment to be effective, participants must complete extended periods of treatment and follow-up care. Residential programs require participants to live onsite at the treatment facility. Intensive outpatient programs may require half or full-day sessions at least five times per week for months with aftercare lasting up to 2 years [67]. Dropout rates tend to be 50% by 3 months, and 80–90% within a year of entry [61]. In four large longitudinal cohort studies conducted from the 1970s to 1990s, which included 70,000 people with SUDs entering residential or outpatient treatment (Drug Abuse Reporting Project, Treatment Outcome Prospective Study, Drug Abuse Treatment Outcome Study, and National Treatment Improvement and Evaluation Study), the length of time in treatment was predictive of posttreatment outcomes. Treatment of less than 90 days appeared to be ineffective, and outcomes improved proportionally with longer length of treatment [61]. Additionally, in the past, some therapeutic communities used aggressive confrontational approaches that may be unpalatable for many people with OUD [68].

These barriers to care prevent OUD treatment uptake and contribute to premature cessation. Availability of and access to OUD treatment are prerequisites for treatment use, but models of treatment delivery must also be acceptable. The next section will review studies assessing patient attitudes toward different OUD treatments, highlighting patient preferences for treatment and informing modifications that could make OUD treatment more patient-centered.

Patient Perceptions About Treatment

No single treatment approach will be acceptable to all people with OUD. Some may prefer to avoid agonist medications, which produce physical dependence, while others may not want to leave home for extended periods of time. In general, people with OUD should have their choice of evidence-based treatments. Though research

on patient preferences is somewhat limited, there are a sufficient number of studies to make some recommendations for patient-centered modifications. This section will review some of the available data by treatment modality.

Methadone Maintenance Treatment

MMT has been available in the United States since the 1960s. In comparison to therapeutic communities, a greater proportion of people referred to MMT actually initiate treatment, which suggests better acceptability [69]. However, many people enrolled in or considering MMT also express ambivalence about the treatment and question its safety [41, 65]. Some of the negative attitudes toward MMT concern the pharmacologic effects of methadone (development of physical dependence, difficulty stopping the medication, effects on bone health or overdose risk, etc.), while others concern negative stereotypes about the type of people who enroll in MMT [41, 65]. One qualitative study described how MMT patients resented the intrusion of treatment into their daily life. Rigid program requirements, such as picking up medication daily, were seen as a "hassle" and overly controlling [65]. Inflexible program rules, hours, and pick-up schedules have also been reported as the reason for conflict with counselors and premature discharge from MMT [66]. Some patient preferences for improving MMT that have been published include requiring fewer visits for medication pick-up, increasing empathy from providers and staff, offering additional social supports with treatment, and assuring patient participation in shaping the goals, course, and nature of treatment [41, 65, 70]. The structured environment of OTPs helps some MMT patients regain stability, but daily program attendance can be burdensome.

Buprenorphine Maintenance Treatment

Office-based buprenorphine treatment has been increasingly utilized since its approval in 2002, with treatment uptake outpacing increases in MMT [71]. Several qualitative studies have reported that buprenorphine-treated patients prefer the medication to methadone, because they perceive that it has fewer side effects, withdrawal is less severe when the medication is stopped, it blocks the effects of illicit opioids, and it is preferable to receive treatment at a doctor's office in comparison to an OTP [72–74]. One patient satisfaction study reported that buprenorphine patients with weekly medication pick-up and less frequent counseling requirements reported better satisfaction than patients with thrice weekly medication pick-up and more frequent counseling [64]. Participants most highly rated "medication" and "being treated like a patient instead of a drug addict" as the most helpful parts of treatment [64]. Another qualitative study reported preferences of patients prescribed buprenorphine at a community health center [75]. Patients believed that treatment should be voluntary, confidential, and there should be shared decision-making about treatment between providers and patients. In addition to the medication, patients

also valued the psychosocial components of treatment and desired a nonjudgmental space where they could share their successes and challenges with recovery [75].

Naltrexone Maintenance Treatment

Though long-acting injectable naltrexone may be a good treatment options for people who have completed medically managed withdrawal from opioids and prefer to remain opioid-free (in comparison to opioid agonist treatment), there is limited data regarding patient-level factors associated with choosing or continuing long-acting naltrexone [16].

Psychosocial and Behavioral Treatments

Patient-centeredness is also important for behavioral treatments. Addiction is characterized by compulsive substance use, negative consequences, and loss of control [76]. Some studies have demonstrated dysfunction in brain areas involved in self-control, motivation, and learning [77]. Therefore, even when people with OUD do not want treatment, coercion into treatment may be ethically justifiable, because involuntary treatment can still be effective and the manifestations of OUD may impair judgment [19]. A full discussion of the ethics of involuntary treatment is beyond the scope of this chapter, but whether people enter treatment voluntarily or involuntarily, the actual OUD treatment delivered can be more or less patient-centered.

Starting in the 1960s, aggressive confrontation was used in some therapeutic communities as a strategy to "break down" behaviors that were thought to reflect denial or other psychological defense mechanisms that rationalized continued substance use. However, a review of 40 years of research on aggressive confrontation was unable to identify evidence supporting the effectiveness of this approach [68]. An empathic and supportive approach to counseling is preferable, because when patients express resistance during counseling sessions, there is low likelihood of subsequent behavioral change [78, 79]. In a study conducted at a residential treatment program, participants were asked to describe positive and negative traits that they perceived in addiction counselors. Among the positive traits were understanding, concerned, caring, experienced, and honest. Among the negative traits reported verbatim were asshole, can't relate, dishonest, treat like children, and uneducated [80]. In a study of adolescents' attitudes toward 12-step groups, participants reported finding several aspects of group treatment valuable, which were not unique to the 12 step-approach: universality of their experiences or not feeling alone; positive encouragement and support; instillation of hope; and catharsis or having a place to talk and express their feelings [81].

Considering all treatment modalities, patients appear to prefer OUD treatment approaches that are voluntary, supportive, and instill hope. Patients prefer treatment providers who are empathic, experienced, and honest. Patients also expressed the

desire to be included in decisions about their treatment and appreciated private and confidential spaces where they could express their feelings. Though different types of counseling were viewed as acceptable, and psychosocial counseling is an important adjunct to opioid agonist treatments, requiring more clinic visits and counseling sessions may turn some people off from OUD treatment. Empathy, support, and patient-centeredness could be emphasized within all models of OUD treatment.

Recommendations

Drawing on known barriers to care, reported patient preferences, and examples from the literature, there appear to be numerous ways to increase OUD treatment availability, accessibility, and acceptability. The following section will review modifications for OUD treatment models that move toward a more patient-centered model of care.

Methadone Maintenance Treatment

Expediting treatment entry and reducing program waiting lists would improve access. Ideally, OUD treatment should be available on demand when someone expresses readiness to enter treatment. Rapid intake into methadone maintenance treatment has been shown to increase treatment uptake and should happen on the day of referral [82, 83]. However, treatment on demand is not always available, and has been less commonly available for indigent patients and for MMT in comparison to other types of SUD treatment [84].

Psychosocial counseling complements and enhances MMT, but mandatory counseling can also be seen as a burden. Reducing the frequency of mandated counseling or making the counseling more patient-centered could increase treatment utilization and therefore effectiveness. A landmark clinical trial demonstrated that patients who received MMT plus psychosocial counseling had superior treatment outcomes to patients who received MMT alone [85]. However, a 2011 Cochrane systematic review concluded that adding more intensive counseling interventions to MMT with standard psychosocial counseling was not associated with improved treatment retention or substance use outcomes [86]. One clinical trial compared a "patient-centered" approach to counseling (i.e., counseling was voluntary and counselors were not responsible for enforcing clinic rules) to standard counseling and found that treatment outcomes were similar [87]. Counselors who were queried about the patient-centered approach reported that it allowed for discussion of a wider range of topics during counseling sessions, but also required new strategies to engage patients [88]. Additional research should establish ideal amounts of and approaches to counseling to support individuals in MMT.

Models of MMT outside of OTPs, similar to office-based buprenorphine treatment, could reduce the stigma of MMT. Other countries allow primary care providers to prescribe methadone for OUD treatment. In Canada, the deregulation of

methadone in 1996 was associated with a substantial increase in treatment uptake, which in turn was associated with reductions in HIV incidence and all-cause mortality [89–91]. In the United States, two clinical trials of office-based MMT demonstrated promising results: higher treatment retention and patient satisfaction and similar or lower rates of substance use than MMT at OTPs [92, 93]. Two other evaluations of MMT in primary care showed high treatment retention and patient and provider satisfaction and little illicit substance use [94, 95]. Office-based MMT would require legislative change in the United States [96].

Low-threshold MMT models could also increase accessibility and acceptability for people who are precontemplative about stopping illicit opioid use. Low-threshold MMT is characterized by absence of waiting lists, acceptance of individuals freely leaving and restarting treatment, and tolerance of continued substance use. This approach would target people with OUD whose primary treatment goal is not abstinence [97, 98]. Low-threshold MMT has been associated with reductions in overdose mortality, all-cause mortality, high-risk injection practices, and criminal activity in other countries, but it is not standard practice in the United States [99–102].

Buprenorphine Maintenance Treatment

Improving availability, access, and acceptability of office-based buprenorphine treatment will require additional certified prescribers, fewer insurance restrictions, and models of treatment that offer programmatic structure and support without creating onerous requirements for patients.

Allowing patients to start treatment at home can remove one barrier to care. Traditionally, buprenorphine "induction" has required in-office observation where patients attend a clinical appointment in opioid withdrawal, so that clinicians can assess their level of withdrawal and administer the first dose of medication [103]. This requirement creates challenges for patients and providers, and likely prevents people with OUD from initiating treatment in primary care [104]. Home inductions are a patient-centered alternative where the clinician provides instructions on self-assessment of withdrawal symptoms and plans for titration of buprenorphine dosage at home. Evidence supports the safety, feasibility, and effectiveness of home-inductions [105–107]. Patient-centered treatment induction could lead to increased OUD treatment uptake.

Removing mandatory counseling requirements could also improve the acceptability of office-based buprenorphine treatment. Psychosocial counseling combined with opioid agonist treatments is beneficial for many patients, and can explore the broad life-changes necessary for recovery. However, when many counseling visits are required in order for patients to receive medication, it can create an artificial barrier to care. Four well-designed clinical trials of buprenorphine maintenance treatment have compared standard treatment (medication management with 15 minutes of focused counseling) to standard treatment plus more intensive behavioral interventions (cognitive behavioral therapy, SUD counseling, and contingency management) and could not demonstrate that intensive behavioral interventions

improved treatment outcomes [108–111]. Observational studies do suggest that buprenorphine patients who better engage in psychosocial counseling or attend self-help groups have better treatment outcomes, but these findings could be driven by selection bias [112, 113]. Ultimately, targeting more intensive counseling to patients' specific needs (e.g., mental health counseling for patients with comorbid psychiatric illness) may be a better way to provide psychosocial support than creating universal mandates for counseling that do not consider patient needs.

Buprenorphine treatment can also be implemented in lower threshold clinical settings, which may improve access and uptake of treatment. One study compared office-based buprenorphine treatment outcomes in a homeless clinic and traditional primary care practice and found that patients at the two sites had similar treatment outcomes [114]. People with OUD who attend syringe service programs have expressed high-levels of interest in buprenorphine treatment, but would prefer to receive care at the syringe service program rather than being referred to primary care or OTPs [115]. Pilot studies have demonstrated feasibility of buprenorphine treatment at syringe service programs [116, 117]. A pilot program in San Francisco has gone one step further, conducting street outreach to homeless individuals and providing buprenorphine prescriptions on demand. While there may be challenges regarding treatment retention and concomitant illicit substance use in these settings, lowering the threshold to program entry could better engage a high-risk, out-of-treatment group, when referral to treatment is unlikely to work.

Psychosocial and Behavioral Treatments

Nonpharmacologic treatments also must be available, affordable, and acceptable, because not all people with OUD will be willing to use medications for treatment. The fragmentation of the health-care system with separate systems for general medical care and substance use disorder treatment impedes access to care and reinforces the stigma that substance use disorders are different than other chronic health conditions [12]. Integrating behavioral treatments for mild or moderate OUD into primary care or other general medical settings may be more desirable for patients than attending specialized substance use disorder treatment programs. However, residential and outpatient treatment facilities will likely still be necessary for people with more severe OUD who require more intensive treatment for behavioral treatments to be effective.

Assuring that treatment providers use evidence-based practices will improve quality of care and likely acceptability of behavioral treatments. Many residential and outpatient treatment programs use abstinence-based counseling and education, which is delivered by staff members with limited professional training and supervision [25]. Staff turnover can also be problematic at programs [118]. There are several evidence-based treatments, including cognitive behavioral therapy, contingency management, motivational enhancement therapy, and family therapies, which could be applied to patients at all stages of change regarding illicit opioid use [12]. People with OUD who seek treatment should receive evidence-based treatments delivered by an appropriately trained workforce.

A strong provider-patient relationship can keep people with OUD engaged in treatment. Empathy, honesty, and acceptance are patient- or client-centered attributes. Counselor empathy is associated with better treatment outcomes even when delivering standard manualized behavioral interventions [119]. In one study, patients' attitudes toward their counselors were associated with longer retention in substance use disorder treatment, which is essential for successful treatment [120]. Motivational interviewing is a patient-centered and nonjudgmental approach to treatment with evidence for efficacy [121]. In particular, motivational interviewing is an appropriate approach to maintain engagement with people who are not ready to stop illicit opioid use.

Tailoring treatments for specific groups may also result in better treatment outcomes. People should receive treatment in their preferred language, and low literacy adaptations may be necessary for program materials and content. Women are less likely than men to enter SUD treatment, and may face greater stigma in seeking care due to societal expectations of women and mothers [122]. Women-focused treatment includes women in provider roles, has gender-specific content, and creates a safe environment for trauma survivors [123]. Gender-specific content may focus on caretaking roles, intimate partner relationships, exposure to trauma, and co-occurring psychiatric illness [123]. Sexual orientation and gender identity may also affect experiences with substance use disorder treatment, and LGBTQ-focused treatment could improve acceptability [124].

Differences in Care Versus Treatment

Available, accessible, and acceptable models of OUD treatment are greatly needed, but we also believe that patient-centered models of OUD care should engage people who remain ambivalent about starting OUD treatment. People who are precontemplative about stopping opioids can still benefit from health services directed at preventing or reducing health risks, including overdose, infection, social isolation, and incarceration. Syringe exchange services can reduce transmission of HIV and HCV (see Chap. 8). Medical care, including novel antiviral therapies, can manage or cure these infections. People with OUD – like all populations – benefit from routine health-care maintenance, including immunization and age-appropriate cancer screening. Trauma-informed care and peer support, which could be delivered outside of traditional health-care settings, improve mental health and reduce social isolation. Therefore, we define OUD "care" more broadly than OUD "treatment" that is only directed at reducing opioid use. Prevention, harm reduction, and health promotion should be components of an ideal care delivery model for people with OUD. However, people with OUD rarely have consistent access to care settings where they can receive these critical health services.

High-threshold models of OUD treatment are often narrow, delivering targeted interventions over short periods of time, with provider-defined treatment outcomes, such as abstinence, and require improved outcomes to continue treatment. These OUD treatment models, such as OTPs or therapeutic communities, are often separated from other health-care services. While high-threshold OUD treatment models provide structure and accountability, they also select for highly motivated patients

Table 10.2 Differences between traditional models of opioid use disorder (OUD) treatment and proposed model of OUD care

	OUD care	OUD treatment
Location	Community-based programs, harm reduction agencies, overdose prevention sites, primary care	Opioid treatment programs, therapeutic communities, intensive outpatient programs, primary care
Threshold for entry	Low threshold: fewer rules/ requirements, enter/exit care as needed	High threshold: more rules/ requirements (e.g., abstinence), waiting lists for entry
Primary goals	Engagement, retention, improvements in health	Reduction in substance use, abstinence
Tolerance of substance use	No requirement for abstinence	Ongoing substance use necessitates increased treatment intensity or program discharge
Patient-provider relationship	Shared-decision making, patient-centered goals	Mixed, including provider-centered and patient-centered goals
Intensity of treatment	Patient determined	Based on standard assessment; often daily contact at initiation
Time frame	Long term (years)	Short or intermediate term (3–12 months)
Target population (based on stage of change)	Pre-contemplative, contemplative, preparation, maintenance phase	Action phase

who can navigate complex systems and adhere to strict rules. Expanding access to OUD treatments only through high-threshold models may not greatly improve treatment uptake. Due to the chronic relapsing nature of OUD, long-term engagement in care is a more appropriate goal than completion of short-term treatment with the expectation of a "cure" (Table 10.2).

In moving toward a more patient-centered model of holistic care, we propose several essential components. To maximize engagement, care models should have a low threshold for entry and create warm and welcoming spaces that "meet people where they are" in relation to their substance use. The care models should offer services to meet basic needs (food, respite, peer support). For people who also seek health-care services, these models should offer individualized assessment of health risks – including harms posed by ongoing substance use – and explore the person's goals regarding risk reduction. Harm reduction services should include but not be limited to peer support, respite, syringe exchange services, supervised consumption, overdose prevention counseling, HIV and HCV testing and treatment, mental health services, and access to intermittent or continuous opioid agonist treatment if desired (see Chap. 8). To maximize retention, care should be easily accessed in an as-needed or drop-in basis, and a person's readiness to engage should determine frequency of contact with the health-care team. These care models should accept that people may continue to use substances while engaged in care, and ongoing substance use should not be a reason for discharge. As peoples' lives stabilize or as their goals change, they may wish to transition to a different setting – perhaps one with more structure – but they should retain access to a low-barrier care setting should they ever need it in the future.

The ideal setting for a low-threshold patient-centered model of OUD care is unclear. There are few places where people who are actively using substances can maintain regular contact with a health-care team. Low-threshold treatment programs could develop within the traditional health-care system, complementing higher-threshold treatment programs. Primary care sites could adapt their practices (e.g., flexible hours instead of scheduled appointments) to improve access to care. Supportive housing models that do not evict residents for actively using substances can offer onsite medical, mental health, and harm reduction services. Safe consumption spaces (or supervised injection facilities or overdose prevention centers) that provide protected, hygienic locations for substance use may also have an onsite health care team [125]. As locations are developed to deliver low-threshold OUD care, a new harm reduction inspired patient assessment will also be needed to maximize engagement and attendant health gains.

Conducting a Patient-Centered Assessment

As noted above, people with OUD who are ambivalent toward reducing or stopping substance use can still benefit from engagement in health services. Patient-centered assessment, which does not make future care contingent on reducing substance use, is critical for engagement and retention. We have developed a guide for patient-centered assessment. Figure 10.1 presents steps that are necessary to establish a substance use history and patient-centered goals of care.

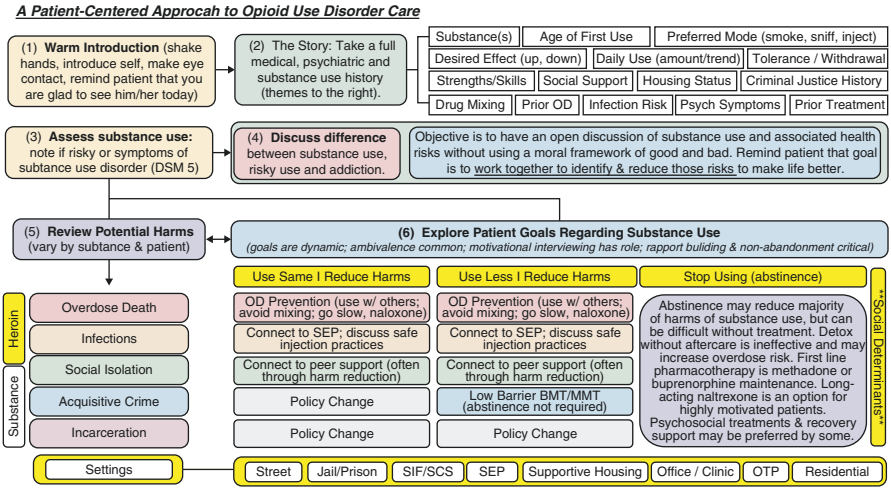

Fig. 10.1 A patient-centered approach to opioid use disorder care. (OD overdose, DSM5 *Diagnostic and Statistical Manual*, 5th edition, SEP syringe service program, BMT buprenorphine maintenance treatment, MMT methadone maintenance treatment, Detox detoxification or medical managed withdrawal, SIF/SCS supervised injection facility/safe consumption site, OTP opioid treatment program)

1. *Warm introduction*: The clinician introduces themselves and seeks to establish a warm, nonjudgmental rapport. The site of OUD care should be able to meet the patient's immediate needs, providing food, community, respite, and other concrete services.
2. *The story*: The clinician should take a full past medical, psychiatric, and substance use history, exploring substance use as it relates to physical and mental health. The history should include current and past substances use, criteria that establish a diagnosis of OUD (e.g., craving, consequences, etc.), experiences with SUD treatment, and also the social context of their substance use (negative or positive effects on family, housing, employment, etc.).
3. *Diagnosis*: The clinician should apply diagnostic criteria (*Diagnostic and Statistical Manual*, 5th edition) to determine whether the patient has a substance use disorder.
4. *Explain the diagnosis*: Patients may be unfamiliar with the differences between addiction and risky substance use, which does not reflect addiction but puts them at risk for harms. Discussing substance use and related terminology in nonjudgmental ways can create an open dialogue about substance use without normalizing it or minimizing how the substance use has caused harms to the patient or others. This discussion can be an opportunity to focus on the harms of substance use without using moralistic frames of whether substance use is good or bad.
5. *Review experienced and potential harms*: Harms will differ for each patient depending on the substances that they are using and their social context. Reviewing harms to the patient and their community establishes targets for behaviors that the patient would like to change. Having patients highlight the harms that are most concerning to them can be an opening for clinician-patient partnership in establishing goals of care and treatment.
6. *Establish patient-centered goals and a strategy to reduce harms*: Goals and strategies will differ depending on the patient's stage of change regarding substance use. Specific strategies can be tailored to patient need based on the harms that are most concerning to them. Treatment and harm reduction should be offered whether the patient desires to stop, cut down, or continue the same level of substance use. Strategies may include referral to traditional OUD treatment or community harm reduction agencies. Acceptability of specific OUD treatment modalities, such as medications or intensive outpatient programs, will differ for different patients. Connecting patients to peer support can address social isolation and despair. In the broader context of OUD care, timely treatment of soft-tissue infections or exacerbations of mental health conditions may take priority over reducing or stopping substance use.
7. *Targeted Health Interventions*: For patients with goals of stopping substance use, more intensive services or transition to a different care setting could be provided. For patients with goals of reducing opioid use, low-barrier pharmacotherapy, which does not make abstinence from illicit substances a condition of treatment, may be effective. For patients with goals of reducing harms while continuing substance use, harm reduction counseling and referral for available community services would be most appropriate. Figure 10.1 also highlights that policy

change, such as reducing use of incarceration to address substance use, will also be necessary to fully address the harms related to substance use. We believe that ongoing engagement in OUD care, even if it does not explicitly include OUD treatment, can reduce many of the harms associated with OUD. It also creates opportunities to deliver immunizations, cancer screening, and other critical health services not explicitly related to substance use.

Our approach to patient-centered assessment is not intended to replace more formal assessments, such as the Addiction Severity Index, which are well established for clinical care and research [126]. Instead, our guide is intended to help clinician match treatment and harm reduction services with individual patients' goals. Our approach is unique, because ongoing substance use or ambivalence toward OUD treatment is not a contraindication to continued care. People with OUD often fear that speaking openly about their substance use will lead their care providers to abandon or "give up" on them. Establishing patient-centered goals prioritizes engagement and retention in care over abstinence. An overall commitment to reduce harms, either through harm reduction or abstinence, should guide the health-care team.

Challenges

Creating a more patient-centered model of OUD care would have many benefits, but lower threshold models that increase treatment uptake could also present challenges to optimizing OUD treatment outcomes. In general, people enter OUD treatment when they have had serious consequences from their opioid use and desire change. If less intensive and structured OUD treatment models were also less effective than standard approaches, then the motivation leading someone to enter treatment could be squandered. If retention in care is not accompanied by improvements in health status and reductions in harms, then long-term retention and engagement in care would be insufficient treatment goals. Specific to opioid agonist treatments, medication diversion could lead to social harms if diverted medication resulted in increased OUD and overdose in the community. If low-threshold models of OUD treatment also had higher rates of medication diversion, individual patient interests may conflict with public health and safety interests. Thus, low-threshold models of OUD treatment should be assessed for safety; however, if the population targeted is people who are resistant to entering standard OUD treatment models, then an appropriate comparison would be receiving no treatment at all.

People with OUD often have comorbid medical or mental health conditions and complex multidimensional needs, which require many resources. Formal decision support tools, such as the American Society of Addiction Medicine patient placement criteria, help clinicians develop a multidimensional treatment plan and recommend an appropriate level of care [127]. However, patients may be unwilling to participate in the level of care deemed to be most appropriate. Nonetheless, if novel settings for OUD care are unprepared to meet these multidimensional needs, then patient outcomes could suffer and providers could develop professional burnout.

Public and private insurers may be unwilling to cover health services provided outside of the traditional health care system, so new payment models may be necessary. Additionally, assuring appropriate training and credentialing of OUD care providers would require oversight. We have proposed collaboration with harm reduction agencies and peer recovery specialists, who do have experience meeting the multidimensional needs of people at high risk for harms from illicit substance use; however, some clinical scenarios, such as management of alcohol withdrawal, would be best addressed in medical settings with an appropriate level of care.

Even with more acceptable approaches to OUD treatment, people with OUD could remain ambivalent about opioid use, and some level of coercion, such as pressure from loved ones, may be necessary to increase treatment uptake. Ultimately, though, we believe that people with OUD, especially those who are precontemplative or contemplative about stopping illicit opioid use, need more welcoming settings where they can engage in OUD care. Traditional OUD treatment models can become more patient-centered, and lower-threshold models of treatment would complement, not replace, higher-threshold or more intensive models of OUD treatment.

Conclusions

Meeting the needs of people with OUD will require models of care and treatment that are available, accessible, and acceptable to people with OUD. Though many people with SUDs enter stable recovery without using formal treatment, many barriers to care do exist for people who want and could benefit from evidence-based OUD treatments. Societal change is needed to reduce stigma regarding OUD and agonist treatments. Policy change is needed to make the full spectrum of OUD treatments more available and affordable in every community. Modifying OUD treatment models to be more patient-centered could also increase treatment uptake and effectiveness by improving acceptability and desirability of treatment. Like stigma and policy change efforts, which will require input and leadership from people with OUD, patients' experiences and preferences regarding OUD care and treatment should also inform creation of more patient-centered models of OUD care and treatment. We have proposed one novel approach to patient assessment and OUD care that seeks to increase health care engagement, including preventive care, OUD treatment, and harm reduction, but there are many paths to recovery. There will be no easy way to stem the increasing harms from the opioid epidemic, but bringing people into care is an important first step.

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Prescribing, Prescription Monitoring, and Health Policy

11

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In 2017, nearly 11.1 million individuals in the United States reported past-year misuse of opioid pain medications, with 36% obtaining the opioids through a prescription [1, 2]. The number of opioids prescribed increased fourfold from 1993 to 2013, and by 2014, 61% of all drug overdose deaths involved opioids, including both prescribed and illicit products such as heroin [3–5]. Prescription opioid-related overdose deaths more than quadrupled in the United States from 1999 to 2017 [6].

Over the last decade, there has been a concomitant, parallel rise in the number of persons exposed to and overdosing from illicit heroin, fentanyl, and carfentanyl [7].

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Prescribed opioids have declined among drugs found in legal seizures since 2012, and poisoning events with licit and illicit opioids often involve multiple, other substances and low doses of prescription opioids [8, 9]. Since 2012, these illicit and diverted substances have been implicated, increasingly, in opioid-related deaths [10, 11]. By 2015, nearly 850,000 individuals in the United States reported past-year heroin use [2]. Corresponding increases in rates of heroin use and 115 daily opioid-related overdose fatalities not only have caused deleterious consequences to families and communities but have incurred more than $75 billion annually of healthcare and societal costs [5, 12–16].

It thus is not surprising that with the rise of heroin and diverted opioids, there has been an increase in the number of persons diagnosed with opioid use disorder. The volume of prescribed opioid medications likely played a role in increases in opioid use disorder and other illicit substances. Among persons aged 12–49 reporting a first instance of heroin use in the National Survey on Drug Use and Health (2002–2011), 80% reported prior nonmedical use of prescription opioids on at least one occasion [17]. There are also important sex and gender differences in opioid-prescribing patterns in the United States: women have seen a sharper increase in the percentage of deaths due to opioids when compared to men [18]. Women are more likely than men to experience chronic pain, more likely to experience their pain as severe, and more likely to be prescribed opioids for pain management [19, 20]. Women are also more likely to receive high doses of prescription opioids than men and to move from first use to problematic use, as well as move more quickly to injecting drugs [21, 22].

From 2001 through 2013, the number of US citizens diagnosed with opioid use disorder doubled from 0.4% to 0.8% related to opioid prescriptions and nearly tripled from 0.2% to 0.7% related to heroin use [23, 24]. By 2016, the National Survey on Drug Use and Health found that 2.1 million Americans had opioid use disorder [25]. All segments of the US population are affected. For instance, the number of infants born to mothers with opioid use disorder has quadrupled with a parallel rise in infants diagnosed with neonatal opioid withdrawal syndrome [26, 27]. Thus, while US policy efforts focus on the "opioid epidemic," the United States is now mired in an "opioid addiction epidemic" [28, 29].

The ultimate cause of this dramatic increase in opioid-related morbidity in the United States is a matter of some debate. Plausibly, the causes of the "opioid epidemic" are multiple. A surplus of prescribed opioid medications contributed to the problem; however, the surplus itself reflects several contributors. In part, pharmaceutical companies and distributors pushed prescribers [30–32]. Their culpability in overaggressive marketing of the safety and effectiveness of opioids has spurred extensive civil and criminal litigation [33]. At the same time, healthcare prescribers contributed to a societal-level oversupply of opioids. For example, pain scores were often treated as a treatment quality and clinical performance metric, which incentivized prescribing [34, 35]. From 1995 through 2010, control of pain was prominent emphasized priority ("pain is the fifth vital sign") [36]. But a response pivoted on resolving pain with prescriptions did not emerge in isolation.

The window of opportunity for aggressive pharmaceutical marketing was itself the result of sequential, well-remarked collective shortfalls in pain education across the health professions, low levels of support for multidisciplinary pain care [37], and health professionals who were neither trained nor compensated to care for complex combinations of medical and psychological comorbidity that typically present with severe chronic pain. The relative lack of healthcare providers' expertise, training, and education in addressing overdose, addiction, pain, and mental health comorbidity likely also contributed. From this standpoint, a collective failure in the health professions and in the US system of health care created a target population of clinicians and patients who were predisposed to embrace a simple, commercial, prescription-based solution for a complex problem.

The drastic increase of persons with prescription opioid use, misuse, and opioid use disorder prompted myriad public health and clinical interventions to curtail opioid-related harm. These approaches are examined in the following domains: (1) initiatives to curtail opioid prescribing, (2) initiatives to monitor opioid prescribing, and (3) public policies and initiatives to confront opioid use, misuse, and opioid use disorder.

Curtailing Prescribing

With the observation that many persons with opioid use disorder started with potentially prescribed opioids, efforts to curtail and control opioid prescriptions emerged as a primary policy response to address opioid-related morbidity and mortality in the United States [38]. Both the lay and academic press reinforced the rationale that reducing the prescribed opioids in society would yield reductions in diversion, in accidental and intentional overdose, and in the incidence of new opioid use disorder, with minimal risk of harm [38, 39]. But a pathway—or some guidance for practitioners—was needed to inform opioid-prescribing practices.

Paramount in this approach was the effort to reexamine and reinforce safe and effective opioid prescribing. In 2016, the US Centers for Disease Control and Prevention (CDC) published the "CDC Guideline on Prescribing Opioids for Chronic Pain." This landmark document examined the indications for initiation, continuation, dosing, and discontinuation of opioids. Guided by CDC's chosen experts, the Guideline offered 12 recommendations. The Guideline recommended that non-pharmacologic and non-opioid treatments be prioritized as first-line treatments for pain and for chronic pain, reflecting evidence that opioids are not, on average, superior to other options [40, 41]. It urged caution when considering doses above thresholds of 50 and 90 daily morphine milligram equivalents (MME). It suggested 3- and 7-day restrictions on opioids for acute pain. For patients already receiving long-term opioids, the Guideline suggested that decisions to taper or discontinue be guided by an individualized consideration of ongoing harm and benefit to each patient. That recommendation, for an individualized decision, credibly aligned with a lack of evidence to support forced opioid reductions as either safe or effective [42, 43]. The Guideline's nuanced language "should have mitigated risk of calamitous care decisions" [44].

The Guideline, however, was not immune to critique on scientific grounds. As Kertesz and Gordon observed:

> "The absence of evidence stronger than observational for all but one recommendation (medications to treat opioid use disorder) was sobering. Also, it emphasized relative rather than absolute risk calculations as the basis for clinical management, an approach susceptible to framing bias [45, 46], particularly when what matters for a patient is the absolute risk of a medication versus alternatives for a condition that involves relentless suffering…The CDC Guideline was characterized by nuance in its language [47] and secrecy in its development [48] …Additionally, the Guideline's emphasis on opioid dose (milligram morphine equivalents (MME)) as the core driver of opioid risk was unduly narrow… The dose-risk correlation in observational studies [49, 50] obscures the independent impact of risk factors that correlate with dose escalation. These include psychological vulnerabilities, race, and polypharmacy [51–54], which in turn multiply (or, in their absence, reduce) overdose risk by factors of 2 to 20 [44, 51, 53]."

While the Guideline could have spurred, under ideal circumstances, a cautious and individualized recalibration of US opioid prescribing, that ideal was not consistently met. Instead, the Guideline's language was interpreted by government and commercial stakeholders to enforce strong regulations, legal warnings, mandates, incentives to restrict healthcare providers' initiation of opioids, and prescription durations and ultimately to force dose reductions in opioid recipients, regardless of the human outcomes [47]. Regulatory bodies, pharmacy chains, and commercial payers mandated dose and duration restrictions in ways that often foreclosed the type of individualized risk-benefit decision-making emphasized in the Guideline itself or promoted by its authors [55–58]. For example, quality metrics were advanced that counted the number of patients above a dose threshold of 120 morphine milligram equivalents as adverse performance indicators [59], regardless of whether the patient's care included the kind of individualized balance of risk and benefit called for by the Guideline.

Federal authorities issued formal warnings to physicians based solely on the number of patients receiving opioids, while pharmacies adopted a range of policies to justify rejection of patients or their doctors [60, 61]. Many payers, regulators, or law enforcement agencies explicitly invoked the authority of the CDC and its Guideline to justify strict binary rules for the determination of quality, coverage, and (for prescribers) legal warnings [62]. Thus, even in situations where clinicians might have assessed that benefits outweighed risks of initiating, maintaining, or continuing the dose of opioids, they found themselves assailed with administrative burdens and professional risk [63, 64]. The CDC Guideline became, in this way, "weaponized."

By mid-2017, 23 states had passed laws limiting prescription duration or dose or authorizing other entities to set limits with effective legal force [64]. The state of Maine mandated that patients on opioids have doses reduced to <100 MME save for narrow exceptions, the nature of which must be reported on every prescription [65]. Private insurers restricted coverage to force doses down as well [66]. In the summer of 2017, two pharmacy firms announced plans to restrict first-time opioid prescriptions to 7 days [57, 67]. Similarly, the National Committee for Quality Assurance (NCQA) and two other agencies imposed metrics in which the number of patients

receiving >120 MME would count against doctors [59], regardless of patient outcomes, even death (which reduces the number of patients on opioids). In so doing, they rejected a petition claiming that a binary dose standard incentivized involuntary tapers and endangered patients, violating the CDC Guideline itself [44, 68].

As of late 2018, the net effect of these efforts at prescription control was mixed. Undeniably, prescriptions, which had begun falling in 2012, fell faster after the 2016 Guideline [69].

Over a period of 5 years after 2012, opioid prescriptions in the United States fell nearly by a fifth [70, 71]. By 2017, they were 19% lower than they had been in 2006 on a per capita basis and 11% lower, overall. A plausible beneficial outcome of these reductions is that prescription opioid misuse had fallen, as divertible pills were less easy to acquire [72]. The US National Survey on Drug Use and Health (NSDUH) reported a 19% relative reduction in past-year prescription opioid misuse from 2012 to 2014 [73] and an 8.7% drop from 2015 to 2016 [25]. On the other hand, the years 2017 and 2018 also saw a rise in reports of harm to health and stigmatization of patients with chronic pain or opioid use disorder—and of the providers that treat them [44]. Media reports commonly featured long-standing opioid recipients who lost access to historic prescriptions and responded variously by seeking care in other settings, overdosing on illicit substances, or attempting suicide [74]. As of early 2019, no large studies had been published outcomes regarding the frequency of such outcomes.

As the drop in US opioid prescribing and reduction in opioid misuse transpired, the rise of heroin use, opioid use disorder, and opioid-related overdoses (as observed in national epidemiological surveys) during the same timeframe drew concern [24, 25]. Plausibly, a more immediate protective impact could be obtained by accelerating treatment expansion for patients with addiction, coupled with enhanced care for opioid-receiving patients with pain [44].

Prescription Monitoring

Historically, the US Department of Justice promoted and implemented Prescription Drug Monitoring Programs (PDMPs) mainly for legal purposes [75]. In this purpose, the Department was able to monitor prescribing practices of clinicians. Over time, PDMPs were increasingly used by clinicians. Today, the tool most commonly available to healthcare providers to monitor patients' receipt of controlled substances is PDMPs. PDMPs capture patient-level prescription fill information to inform monitoring and dispensing decisions and possible intervention [76–83].

PDMP output data is limited in its clinical utility because it does not provide decision support, and users must act on "best judgment" and provide patient care and referrals with a limited evidence base. The introduction of PDMPs, while valuable, has not typically been seamless and could be potentially costly to integrate. Many PDMPs are not integrated into the electronic health record, requiring healthcare providers to both synthesize data from an external web source and document these results within the EHR, an often laborious process that could be fraught with human error.

The evidence on whether PDMPs have reduced harms associated with prescribed opioids is mixed. PDMP programs have demonstrated clear results for reducing prescribing [77–84]. However, PDMP's effectiveness has not been shown in regard to clinical outcomes for persons with opioid use disorder, including rates of overdose, opioid medication misuse, or fills for potentially lethal drug combinations, such as benzodiazepines, for which only descriptive information is available [80, 85–95]. As of early 2019, a small number of studies had begun to examine specific PDMP features and effects of mandating PDMP use [78, 92, 96, 97]. Given these marked deficits of evidence, further investigation is crucial to understand the patient impact of these programs.

While PDMPs can improve the ability of healthcare providers to understand prescription patterns for individuals, they do not provide information on opioid risks and opioid mitigation strategies for a given patient. How PDMP information and output can be automated for presentation to providers within an evidence-based clinical decision support tool is an important question. Some opioid risk assessment and mitigation platforms have emerged, including private commercial products and the Stratification Tool for Opioid Risk Mitigation (STORM) dashboard of the US Department of Veterans Affairs (VA) [98]. Integrating PDMP information and outputs in such a system could improve healthcare providers ability to not only understand opioid prescribing of an individual but has the promise of potentially reducing opioid-related morbidity and mortality.

Health Policy and Health Systems Responses

As an "opioid epidemic" (marked by ubiquitous divertible pills, peaking in 2012) evolved toward an "opioid addiction epidemic" (marked by a surge of overdose mortality in the 6 years that followed, often with heroin or fentanyl), policy responses tended to lag the evolution of the crisis itself. For example, efforts to stem the supply of prescribed opioid medications emerged without similar robust and timely responses to the predicable strengthening of the illicit market that followed. For example, there were efforts to reformulate medications, such as long-acting oxycodone, to be less available to divert (e.g., reduce the ability of a person to crush up and inject the formulation) [61, 99, 100]. Furthermore, state guidelines and early reports from the CDC likely helped to spur doctors to contain distribution of prescription drugs but did not contain the rise of illicit heroin and fentanyl and might well have spurred demand [101–103]. Furthermore, communities encouraged the use of opioid reversal agents (e.g., naloxone) and sought to increase the capacity for addiction treatment [104–108].

The recognition of excess risk associated with opioid therapy for pain has led to several risk mitigation interventions and policies at both the state and federal levels. Many states now have mandated limits or cautions regarding high-dose and long-acting opioid prescribing and benzodiazepine co-prescription, all known factors associated with increased opioid-related adverse events [109, 110]. States are also requiring providers who prescribe opioids to have specific hours of continuing medical education (CME) regarding opioid prescribing and risk mitigation. On the

federal level, FDA initially mandated that both prescribers and patients receive Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS) education for extended-release and long-acting opioids. Lately, FDA has expanded the REMS provision requirement to short-acting opioids [111, 112].

The 2016 US Congressional act named Comprehensive Addiction and Recovery Act (Pub.L.No. 114–198; CARA) outlined a coordinated effort to confront opioid misuse and overuse through prevention, treatment, recovery, law enforcement, criminal justice reform, and overdose reversal. Enactment of CARA has influenced health systems of care. For example, CARA directed the Veterans Health Administration (VHA) to improve opioid therapy strategies in treating veterans under their care and to ensure responsible prescribing practices (Subtitle A Sec 911). In response to the CARA rules, the VHA Office of Mental Health and Suicide Prevention (OMHSP) developed Stratification Tool for Opioid Risk Mitigation (STORM), a web-based dashboard that prospectively prioritized review of VHA patients receiving opioids based on their risk for overdose-related, accident-related, or suicide-related events (collectively, serious adverse events [SAEs]) [113]. The STORM risk prediction model uses patient demographic characteristics (e.g., age, race); medical, psychiatric, and substance use comorbidities; psycho-polypharmacy; and acute healthcare utilization to predict opioid-related SAEs. VHA clinicians can use STORM to identify risk factors and risk mitigation strategies potentially relevant for each patient [98]. Recently, VHA has also mandated interdisciplinary teams at every facility to identify patients at high risk for opioid-related SAEs based on STORM dashboard and integrate their care to prevent adverse SAEs. VHA has also mandated that every facility develop an interdisciplinary Pain Management Team to provide comprehensive care for patients with chronic pain, and every facility is also directed to increase local availability alternative and complementary integrative modalities for pain treatment like yoga, tai-chi, acupuncture, and other "whole-health" approaches. The effectiveness of such risk mitigation strategies is under evaluation now [113, 114].

There is an increasing recognition that increased access to and improvements in the quality of addiction care are needed in the United States. CARA, and other legislative actions, attempted to infuse resources into a US addiction treatment system that needed help. Despite these initiatives, 6.7 million Americans who needed treatment for opioid use disorder in 2016 did not receive it [25]. Historically, addiction care in the United States is hindered by the low quality of its treatment infrastructure, lack of training, and regulatory restrictions [115, 116]. The strain on the United States' specialty addiction infrastructure has opened gaps in the capacity to treat patients with opioid use disorder [29]. Just 27% of national treatment programs surveyed in 2016 offered buprenorphine, and 8.1% offered methadone, despite consensus that medication treatment for opioid use disorder should be universally available [117–119]. Even when medication for opioid use disorder is offered, follow-up can be inadequate, and the quality of care may be poor; and access does not necessary mean quality of care is actually provided [120].

There is a growing recognition that medication treatment for opioid use disorder is the evidence-based, gold standard treatment for opioid use disorder that

reduces illicit opioid use, mortality, criminal activity, healthcare costs, and high-risk behaviors [121–127]. In addition, medication treatment improves patients' quality of life [128–131]. Outcomes generally improve with longer treatment duration; relapse to illicit use and mortality increases when the medication ceases [120, 125, 132–137]. Although US law mandates parity in physical and mental health treatment [138], insurers continue to limit opioid use disorder care [139]. In addition, many insurers require non-pharmacotherapy counseling as a precondition for medication treatment for opioid use disorder, regardless of need [43, 140, 141].

Regulatory burdens exist in confronting the access of treatment of opioid use disorder, and there are calls to reduce these burdens. For example, there are growing calls to limit the education and training required to prescribe buprenorphine for the treatment of opioid use disorder [142, 143]. To confront the growing "opioid addiction epidemic," targeted resources to promote evidence-based treatment, with access to medication treatment, delivered in a quality way, is imperative.

Summary

In response to the enormous challenges of opioid overprescribing and associated adverse impact like opioid addiction and overdose, varied risk mitigation strategies and healthcare policies have emerged at the federal, state, community, healthcare system, and individual-practice levels. Many of these interventions have less than stellar evidentiary support but reflect the legitimate perceived urgent need for response when facing a crisis. As the "opioid epidemic" has evolved into an "opioid addiction epidemic," and more evidence becomes available, many of these interventions are also evolving. It is paramount, however, that the best evidence is applied to inform policy decisions to reduce the harm associated with opioid misuse and opioid use disorder [44, 144, 145].

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Effective Opioid Analgesic Alternatives and Approaches to Pain Management

12

Jenna Goesling and Mark Ilgen

In recent years, policy makers have expressed growing concerns about the extent and consequences of the opioid epidemic in the United States [1]. These concerns reflect the substantial growth in opioid prescribing that occurred over the past 10–15 years [2], the recent rises in heroin and fentanyl use over the past 5 years [3], and the associated increases in opioid-related adverse outcomes, including fatal and nonfatal overdoses [4–6]. Pain treatment advocates helped to shape the initial arguments for increasing opioid prescribing in the late 1990s, and individuals with chronic pain have been disproportionally affected by the opioid epidemic [4, 7]. As awareness has increased recently about the potential risks of opioid overprescribing, the need remains to develop and deliver treatments that effectively address pain and improve functioning in those with chronic pain while minimizing the individual and societal burden associated with opioid use and use disorders.

The present chapter is intended to present a concise overview of the literature on chronic pain treatment, with an emphasis on some of the consequences of, and alternatives to, opioid use. The chapter includes an overview of the extensive literature on non-opioid treatments for pain. Given the broader focus of this book on treating opioid use disorders, the present chapter will highlight what is known about addiction within the context of opioid use for chronic pain as well as a discussion of the potential benefits of non-opioid treatments for those who struggle with addiction to opioids or other substance use disorders.

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A Brief Overview of Chronic Pain

It is estimated that over 100 million people in the United State are living with chronic pain [8]. Chronic pain is frequently defined as persistent and recurrent pain, lasting longer than 3 months or simply put "pain that continues but should not" [9]. Chronic pain is distinct from acute pain in that it persists well beyond the expected healing time and is no longer signaling damage to the body. Once pain becomes chronic, the original source of the pain does not sufficiently explain the persistence and severity of symptoms. While pain is often characterized according to a specific location (e.g., back, head), there are many distinct types of chronic pain (e.g., neuropathic, musculoskeletal). It is helpful to consider the mechanisms of chronic pain, which can be divided into peripheral (nociceptive and neuropathic) and centralized mechanisms. Peripheral pain stems from abnormalities in the peripheral tissue, nerves, or joints, leading to pain sensitivity in specific areas of the body. Knee osteoarthritis and chronic low back pain are classic examples of peripheral nociceptive pain, which is caused by inflammation or tissue damage. Peripheral neuropathic pain, such as diabetic neuropathy, is characterized by damage or dysfunction to the peripheral nerves. Central pain mechanisms operate at the level of the central nervous system (CNS), and these pain states are associated with more widespread pain and other symptoms associated with augmented CNS processing such as poor sleep and fatigue. Fibromyalgia is one of the most common centralized pain disorders [10]. Over the last two decades, this distinction between peripheral and centralized pain states has helped to advance our understanding of chronic pain and is especially critical when considering different treatment options [11].

Chronic pain is the leading cause of disability, and the economic costs are estimated to be upward of $560–$635 billion dollars per year [12]. Low back pain is the most common pain complaint in adults, with 70–85% of people experiencing back pain in their lifetime [13]. In most cases, acute back pain resolves; however, a small percentage of people will develop persistent and chronic low back pain. Researchers have sought to identify risk factors that predict who will go on to develop chronic pain, and several demographic variables are associated with an increased risk including female gender [14], older age [15], and lower household income [16]. Anatomical predictors have proven to be evasive, with almost no correlation between damage seen on imaging and clinical presentation. Psychosocial factors have also been studied extensively and are strong predictors for chronic pain. Chou and colleagues found that the strongest predictors of developing chronic low back pain were maladaptive coping behaviors and having a comorbid psychiatric diagnosis [17].

Treatment options for chronic pain typically include a combination of medication and surgical interventions, with the goal of relieving pain and restoring function. Despite advances in pain management, medical interventions frequently cannot resolve chronic pain, leaving many patients with a significant amount of pain and limited functioning. It is now widely accepted that optimal management for chronic pain includes treatments that address not just the biological cause but also the role of psychosocial factors in the development and maintenance of chronic pain.

Chronic Pain and Opioids: From Panacea to Epidemic

In the late 1990s, the American Pain Society introduced a new slogan, "Pain, The Fifth Vital Sign." This push was in response to significant concerns about pain being underdiagnosed and undertreated, especially in terminal cancer patients. The campaign to recognize pain as the fifth vital sign was a success. In 1999, the Veterans Health Administration adopted it, and the Joint Commission on the Accreditation of Healthcare Organizations (JCAHO; "Joint Commission") made assessment and treatment of pain mandatory for all accredited healthcare organizations by 2001 [18]. Simultaneously Oxycontin, the extended-release version of oxycodone, was approved by the FDA and released to the market in 1996. Oxycontin was heavily marketed by Purdue Pharma as an effective treatment option for chronic pain. Risk of addiction was minimized based on two retrospective studies that became widely cited as evidence that pain protects patients from developing opioid use disorders [19, 20]. With a mandate to treat pain as the fifth vital sign and the availability of a new "safer" opioid, providers began prescribing opioids more frequently to patients with chronic pain. Not surprisingly, the rates of opioid prescribing for the treatment of chronic pain increased dramatically over the next 20 years. From 1998 to 2012, opioid prescriptions doubled, with 200 million opioid prescriptions written in 2012 by providers in the United States.

Today we find ourselves in the midst of an opioid overdose epidemic that has become a major public health crisis. Along with rising prescribing rates, there has been a dramatic increase in opioid overdoses and deaths [5]. Concerns about opioid addiction and overdose are not limited to people using illicit opioids. Despite the early studies that were frequently cited in support of claims of low addiction risks, recent studies suggest chronic pain patients are, in fact, at risk for adverse outcomes, including addiction and overdose [21]. A systematic review in 2008 found varied rates of opioid misuse and addiction in patients with chronic pain, ranging from 0.2% to 3.27%, with rates of aberrant drug-related behavior around 15–20% [22]. Some of the challenges associated with establishing risk stems from the population being studied. For instance, misuse rates are significantly higher in studies that do not exclude patients with comorbid mental health diagnoses and a history of substance use disorder [23]. It follows that in order to justify the risks associated with long-term opioid use, benefit must be clear. Recent systematic reviews of randomized controlled studies found little to no evidence that long-term opioid therapy was associated with improvements in pain, function, or quality-of-life outcomes [21]. This is, in part, because there were no well-controlled studies that followed patients longer than 12 weeks or included a non-opioid control group. A recent study by Krebs and colleagues compared opioid medication and non-opioid medications in patients with osteoarthritis pain over 12 months [24]. Treatment with opioids did not lead to improved functioning compared to non-opioid medication. They concluded that there were no benefits to opioid medication that outweigh the risks of harms associated with opioids.

Given the risks and questionable benefits, there has been a major shift in how opioids are viewed in the context of pain management. In response to the rapidly

changing climate, guidelines for opioid prescribing were revisited in 2009, and several recommendations were made in an effort to reduce opioid prescribing [25]. Broadly, the guidelines aim to prevent new opioid use and reduce the number of patients maintained on long-term opioids. These guidelines also state that even though evidence is limited, "chronic opioid therapy can be an effective therapy for carefully selected and monitored chronic pain patients." In 2016, the Center for Disease Control and Prevention (CDC) updated their guidelines for prescribing opioids for chronic pain and made 12 recommendations [26]. Two key recommendations were that non-opioid therapy is preferred for treating chronic pain and that "opioids should only be used when benefits for pain and function are expected to outweigh risks" [26]. Once a person has been initiated on chronic opioid therapy for pain, opioid cessation may prove to be more challenging than preventing new opioid use. As fewer and fewer patients with chronic pain will be using opioids, physicians and patients will be in need of non-opioid-based treatment for pain management.

As the pendulum rapidly swings from pain control to drug control in response to the opioid epidemic, it is important to take care to reduce the potential harms the changes to opioid prescribing may have on patients with chronic pain. There are still many unanswered questions. For instance, for whom are opioids likely to be most effective? For whom are they most likely to be problematic? How do we assess and treat opioid addiction in patients prescribed opioids for pain management? Finally, as opioids are being prescribed sparingly for chronic pain, what are non-opioid alternatives to managing chronic pain? For millions of patients living with chronic pain and providers who treat these patients, the answers to these questions will have a lasting impact on pain management.

Opioid Use, Physiological Dependence on Opioids, and Opioid Use Disorders

The dialogue on the opioid epidemic has shifted attention to the intersection between pain and addiction [27]. As noted earlier, some of the initial marketing that encouraged greater use of opioids claimed that these medications were associated with low risk of addiction. Newer research indicates that the initial estimates were low and that more individuals who receive opioids engage in some form of misuse of the medications [23, 28]. However, this topic is difficult to study for a number of reasons, including unclear definitions of core constructs and inconsistent use of these definitions in the clinical and research literature. Here, we highlight three core, and sometimes overlapping, constructs that are relevant to the understanding of pain and addiction.

Physiological dependence is the development of tolerance to a substance, where higher doses are needed to achieve the same effect, or where withdrawal symptoms develop during periods of time without the substance. These are biological consequences of longer-term exposure to many substances, including opioids. It is important to note that physiological dependence can occur across species and that sufficient doses of a substance for a long-enough period of time can lead to physical

dependence, without the individual displaying any aberrant behaviors. Thus, a person who receives a regular prescription for a higher dose of opioid can become physiologically dependent even if she/he is fully compliant with her/his recommended dose. This is one reason why it is extremely important for providers to avoid rapid tapers of opioids on those receiving higher doses because these could precipitate withdrawal.

Opioid misuse is the use of a medication in a manner that is different from how the medication is prescribed. The term "misuse" is often used interchangeably with the stigmatized term "abuse," which should be avoided, and the terms "nonmedical use" and "extramedical use" are used instead. Medication misuse can reflect any of the following ways that prescribed opioids may be used in a manner that is inconsistent with how/why they were prescribed: (1) using a greater quantity of opioids than prescribed; (2) using opioids at a greater frequency than prescribed; (3) obtaining medications from someone other than a physician; and (4) using for reasons other than pain relief (either to "get high" or treat another non-pain-related problem) [29]. Thus, many factors may underlie the motivation for prescription opioid misuse. Depending on the specific motivation and extent of misuse, the individual may or may not meet criteria for a diagnosable opioid use disorder (see below).

Opioid use disorder (OUD) is the development of a series of problems associated with the use of opioids. These problems may include, but go beyond, physiological dependence and include symptoms like spending a good deal of time thinking about or consuming opioids, craving opioids, taking in larger amounts or for longer periods of time than intended, continued use despite harmful consequences, etc. [30]. OUDs can be thought of as the more severe end of the continuum of misuse of opioids and, when most severe, are best treated with an opioid agonist, such as methadone or buprenorphine [31].

Because there are clear disincentives for patients to report symptoms of misuse or OUD to their pain treatment provider for fear of losing access to opioids, treatment providers often have an unclear picture of the extent of problems in their patients. Also, even when opioid misuse or OUD is present, these individuals may still suffer from chronic pain.

Beyond Opioids: Evidence-Based Non-opioid Alternatives for Managing Chronic Pain

Given the state of the opioid epidemic and concerns about the effectiveness of opioids for chronic pain, it is now more important than ever to focus on non-opioid alternatives to pain management. Importantly, the most recent guidelines from the Center for Disease Control and Prevention (CDC) recommend against the new initiation of opioids for chronic pain and state that opioids should only be used as a last resort after all other treatment options have been exhausted [26]. Additionally, the guidelines state "nonpharmacologic therapy and nonopioid pharmacologic therapy are preferred for chronic pain" [26]. After decades of managing chronic pain with opioids, we are now standing at a post-opioid crossroad that will shape the course of pain management for the next two decades.

Overview of Non-opioid Pharmacotherapy Treatments

Pharmacological treatments for chronic pain are not created equal, and understanding the range of non-opioid treatment options is particularly important as opioids are used more sparingly as a treatment for chronic pain. Common non-opioid pharmacotherapy options include nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, tricyclic antidepressants (TCAs) [32, 33], selective norepinephrine reuptake inhibitors (SNRIs) [34, 35], and anticonvulsants (gabapentinoids). The first step in selecting medication is to determine the underlying cause of pain (see Table 12.1). Therefore, it is more accurate to think of these medications according to their mechanism of action versus the class of drug. NSAIDs (aspirin, ibuprofen, and naproxen) and acetaminophen (Tylenol) are the first treatment choices for managing acute pain [36]. They are also frequently used as a single agent or in combination with other medications to treat chronic pain. NSAIDs are analgesic and anti-inflammatory and are effective for treating musculoskeletal pain of nociceptive or inflammatory origin, as this is thought to provide the primary analgesic efficacy of this class of drugs. This class of drug is less effective for neuropathic pain [37].

Antidepressants have been used as adjunctive treatment options for chronic pain management for decades. Researchers still debate the underlying reasons that antidepressants are effective for pain, but the leading hypothesis is they improve pain mainly via augmenting activity down descending anti-nociceptive pathways that use norepinephrine and serotonin as key neurotransmitters [38, 39]. Individuals with chronic pain without depression are just as likely to respond to these classes of drugs as analgesics as individuals with depression [40]. That is, these drugs have an independent effect on pain, not because of their antidepressant effects, but rather because the same neurotransmitters serve different functions in different brain regions. TCAs are the most extensively researched and most commonly used antidepressants for pain and include the tertiary amines (amitriptyline, doxepin, imipramine) and secondary amines (desipramine, nortriptyline). TCAs are recommended for multiple pain conditions including both peripheral and neuropathic pain states [41]. The main downside of TCAs is side effects, making their use somewhat limited in certain patient populations. Serotonin and norepinephrine reuptake inhibitors (SNRIs) are increasingly being used for pain treatment. The FDA has approved duloxetine and milnacipran for treating chronic pain, and duloxetine is also approved

Table 12.1 Overview of pharmacotherapy treatment for chronic pain

Types of pain	Pain characteristics	Examples of pain conditions	Analgesic recommendations
Peripheral (nociceptive)	Inflammation or mechanical damage to tissue	Osteoarthritis Rheumatoid arthritis	NSAIDS Opioids
Neuropathic	Damage to peripheral nerves	Diabetic neuropathy Sciatica	Opioids Anticonvulsants
Centralized (non-nociceptive)	Disturbances in central pain processing	Fibromyalgia Irritable bowel syndrome	TCAs SNRIs Anticonvulsants

for treating fibromyalgia. TCAs and SNRIs are recommended as first-line treatment for neuropathic pain [41]. Several recent meta-analyses on selective serotonin reuptake inhibitors (SSRIs) have concluded there is limited evidence for their use to treat pain specifically, but they are recommended for comorbid symptoms of depression [42, 43]. In a recent review of the adverse effects of antidepressants compared to placebo, the authors concluded that at low doses, antidepressants are tolerable when used for chronic pain management [44].

Anticonvulsants, such as gabapentin and pregabalin, are the other classes of adjunctive medications most commonly used for pain management. These drugs are thought to work in the CNS at least in part by reducing glutamatergic activity in ascending pain pathways [45]. The FDA approved pregabalin for diabetic neuropathy and fibromyalgia. It is important to note that the gabapentinoids have misuse potential and may potentiate the risk of overdose when used concomitantly with opioids [46].

Overview of Nonpharmacological Treatments

The Role of Psychological Interventions

Pharmacological agents will likely continue to be used as a first line of treatment for chronic pain for the foreseeable future. However, in recent years, chronic pain is increasingly seen through the lens of the biopsychosocial model [47]. This is because we now recognize that chronic pain is a complex condition that is influenced by physical, cognitive, affective, and interpersonal factors. Because of this, pain management often requires a multidisciplinary treatment model, which utilizes specialists trained in a variety of disciplines (e.g., pain psychologist, physical therapist) [48]. There are numerous psychotherapy options for chronic pain that have been extensively researched. They share many overlapping core concepts, and the more recent interventions aim to address some of the gaps identified after decades' worth of research. In this next section, we summarize the types of psychological treatments that have the best evidence for use in chronic pain.

It is helpful to consider the rationale for including psychotherapy in pain management. Over the years, in spite of advances in treatment, it has become clear that there is rarely a "cure" for chronic pain [49]. As the field has evolved, there has been a shift away from the goal of eliminating the sensation of pain though procedures and medication toward a model that focuses more on improving functioning and self-management of symptoms. Psychotherapies are well suited to address such treatment goals. Additionally, individuals with chronic pain are at risk for comorbid mental health issues, such as depression and anxiety [50]. That is, living with chronic pain can significantly impact quality of life, resulting in negative psychological consequences [51]. Additionally, depression and other mental health comorbidities are known risk factors for those who develop chronic pain [52]. Thus, the relationship between chronic pain and psychiatric comorbidities is best conceptualized as bidirectional [50, 53]. It follows that because psychological interventions

address the behavioral, cognitive, and emotional factors that result from and contribute to pain-related distress, they play a critical role in pain management.

Operant Behavioral Approach

Prior to the 1970s, the biomedical model of pain dominated our view of chronic pain. In 1976, Fordyce introduced a behavioral theory of pain that opened the door for the biopsychosocial model of pain management. Fordyce's model focused primarily on learning processes (classical and operant conditioning) that contribute to the development and maintenance of chronic pain [54]. Specifically, the operant model of pain puts pain behaviors front and center and hypothesizes that the behavioral drive to avoid pain contributes to pain chronicity. Pain behaviors are how we communicate pain (e.g., actions, verbalizations) and are effective for acute pain, but Fordyce argued that, over the long term, they become maladaptive. For example, avoiding painful activity (i.e., a pain behavior), while an adaptive response in the case of acute pain, long-term avoidance of activity will lead to pain chronicity and physical deconditioning [55]. Behavioral treatments for chronic pain have drawn heavily on operant theory and focus on decreasing maladaptive pain behaviors and reinforcing adaptive behaviors through graded patterns of activity, activity pacing, and in vivo exposure. Classic behavioral interventions also teach relaxation skills and address the role of family members in reinforcing pain behaviors. Behavioral therapy has evolved over the years and is rarely a stand-alone therapy. Instead elements of behavioral therapy are used in combination with cognitive therapies, which focuses more on thoughts, beliefs, and expectations [54].

Cognitive-Behavioral Therapy

Cognitive-behavioral therapy (CBT) is the most widely studied psychological intervention for chronic pain and is considered the gold standard for pain management. CBT is a hybrid of Fordyce's behavioral therapy and cognitive therapy. A recent review article concluded that CBT demonstrates small to medium effect sizes compared to standard of care across a variety of clinical outcomes, and it has been shown to be more effective than behavioral therapy [56]. Critics of CBT point to the small effect sizes, diminished effects over time, and a lack of clarity about how CBT works and for whom it works [57]. In spite of these shortcomings, the conclusion from decade's worth of research is that there is good evidence that CBT is effective in improving pain and pain-related problems in the context of chronic pain.

The theoretical framework that informs the CBT model for pain is rooted in traditional CBT but has been modified to meet the unique needs of pain patients. Broadly, the CBT model posits that maladaptive behaviors and cognitions influence pain perception and contribute to pain, disability, and suffering. The mechanism by which CBT is thought to work is through changing behavior and cognition, which, in turn, leads to improvements in pain, functioning, and overall quality of life. For

example, pain catastrophizing (e.g., "This pain is unbearable, it has never been this bad") is a common negative thought and is consistently associated with higher pain and greater psychological distress. According to the CBT model, catastrophizing adversely impacts pain perception, and CBT teaches patients how to replace negative thoughts with more realistic, adaptive thoughts. In fact, one of the most consistent findings in the CBT literature is that the people who benefit the most from CBT tend to be high in pain catastrophizing.

While there is no standard protocol per se and CBT varies in terms of specific goals and treatment, CBT typically includes three phrases: (1) education, (2) skills training, and (3) application of skills. Education is done at the onset of therapy and provides patients with a rationale for why CBT is used for pain and outlines treatment expectations. Another unique aspect of CBT is homework, which encourages patients to practice and apply the skills taught during therapy to their day-to-day life. At the heart of CBT is skills training. Although the skills taught may vary, core CBT skills include relaxation training, behavioral activation and pleasant activity scheduling, time-based pacing, cognitive restructuring, and modifying pain beliefs. Each skill focuses on identifying and changing maladaptive behaviors and thoughts and learning new coping skills in response to pain. Often CBT skills are referred to as "tools" to add to a pain management "tool box." For example, relaxation training is one of the most commonly used behavioral skills in CBT for pain management. Patients are taught how to reduce autonomic arousal by activating the relaxation response through abdominal breathing, guided imagery, and progressive muscle relaxation. Another core behavioral skill is time-based pacing, which teaches patients to rest during an activity based on how long they have been active and not wait until the task is completed to take a break. This skill can be used to prevent patients from overdoing activity on good days, which reduces the risk of a flare-up. Maladaptive thoughts and beliefs are targeted using cognitive restructuring. Here the goal is to identify underlying negative thought patterns about pain and reframe these thoughts with more accurate, adaptive thoughts. Together these core behavioral and cognitive skills shift the focus to adaptive pain-coping strategies and provide a greater sense of control over pain.

Acceptance and Commitment Therapy and Mindfulness-Based Therapies

Acceptance and commitment therapy (ACT) and mindfulness-based therapies are more recent psychotherapy interventions for chronic pain and were developed around the strengths and weakness of the CBT model [58]. Although the research literature is not as extensive as CBT, both are considered empirically supported treatment options for chronic pain. ACT evolved in part out of the recognition that pain often cannot be eliminated and attempts to eliminate pain may not only be impossible but can also lead to additional suffering [58]. Instead, pain is seen as an inevitable part of life and is viewed as something we can learn to accept. In contrast to the way that CBT is often conceptualized, as trying to control or change the

experience, ACT's mechanism of action is through acceptance. For example, in ACT, the goal is to observe unpleasant thoughts, feelings, and sensations as they arise without trying to change them [59]. ACT stresses the importance of engaging in value-based goals that help guide behavior, even when pain is present. ACT-based interventions for chronic pain have been shown to impact a range of clinical outcomes; however, the conclusion from meta-analyses is that ACT does not show superior efficacy compared to CBT [59].

Mindfulness-based therapies include mindfulness-based stress reduction (MBSR) and mindfulness-based cognitive therapy (MBCT). Mindfulness is broadly defined as "paying attention in a particular way, on purpose, in the present moment, and nonjudgmentally" [60]. MBSR is rooted in Eastern philosophy and has been adapted to become an intervention for a wide variety of chronic conditions, including chronic pain. MBSR is typically delivered in a group format over a period of 10 weeks [61]. Similar to ACT, MBSR approaches thoughts not as something to be changed but rather the goal is to learn how to find emotional distance from thoughts through nonjudgmental observation [61]. One core component of MBSR is daily meditation, which is considered a skill that can enhance self-regulatory coping strategies. A recent meta-analysis found that MBSR had a small to moderate effect on psychological outcomes, pain intensity, and coping with pain and stress. Similar to other interventions, the effects of MBSR may differ depending on the pain population, with stronger effects seen in spine pain compared to fibromyalgia and headache [62]. A recent study by Cherkin and colleagues compared MBSR to CBT or usual care and found improvement in back pain and functioning among patients treated with either MSBR or CBT [63]. While both interventions were more effective than usual care, there was no difference between the MBSR and CBT treatment conditions.

Summary of Psychotherapy Interventions for Chronic Pain

The CBT, ACT, MBSR, and operant behavioral approaches described in this chapter are all considered evidence-based interventions for chronic pain. There is no question that psychotherapy plays an important role in optimizing treatment for chronic pain, and there is a consensus in the field that a multidisciplinary treatment approach yields the best outcomes. In order to continue advancing this treatment modality, there are several important questions to consider across all psychotherapy interventions. The benefits of psychotherapy are modest at best, and so far the newer interventions have yet to demonstrate superior effects over CBT. In fact, there is little to no evidence that one treatment approach is superior. Because there is much overlap across interventions, more research is needed to identify which elements of each treatment have the strongest effects. In order to improve treatment outcomes and produce longer-lasting results, the next step is to combine elements from the different interventions. Additionally, every pain patient is different, which suggests that developing personalized interventions that address the unique needs of each individual may enhance treatment outcomes. Finally, one of the challenges with

psychotherapy interventions is treatment availability. To address this, there has been growing interest in adopting alternative delivery platforms, including telephone- and Internet-based interventions, with some preliminary support for delivering CBT, ACT, and mindfulness programs using these platforms [64–66]. There is still room to improve, and developing novel and innovative psychotherapy interventions is critical in our path toward optimization of chronic pain management. In addition, it is important to understand how CBT, ACT, and mindfulness programs function in the presence or absence of other pain treatments (e.g., opioids) and how these treatments may work in those with varying levels of misuse, abuse, or dependence of opioids.

Exercise

Many would argue that exercise should be a first-line treatment for chronic pain. This is due to the extensive literature demonstrating the benefits of exercise across all types of chronic pain [67, 68]. From low back pain to fibromyalgia, exercise improves pain, function, and psychological well-being [69, 70]. Evidence-based exercise programs for chronic pain include a wide range of activities including strength training (anaerobic), flexibility training, aerobic (e.g., walking, running, swimming, dancing), and other movement therapies (e.g., yoga, Tai Chi, Qigong). These categories are not mutually exclusive. For instance, yoga can fall into all four of the categories. Research has shown that the type of activity matters less than finding an activity one enjoys and will maintain. However, in RCTs comparing aerobic exercise to flexibility training in patients with chronic widespread pain, aerobic exercise is superior to flexibility training for improving fitness and decreasing pain [71]. In fact, the strongest evidence is for aerobic exercise, which consistently is associated with decreased pain. A handful of recent studies have looked at movement therapy, and although more research is needed, there is growing evidence that both Tai Chi and Qigong may be beneficial [72]. Often the challenge with exercise is motivating people to be active when activity is associated with pain. Tailored exercise programs are likely the key to enhancing motivation and adherence.

Physical Therapy and Complementary and Alternative Medicine

Physical therapy (PT) is another critical part of multidisciplinary pain management programs, and engagement in PT has been shown to improve pain and physical functioning [73–75]. A PT program typically includes a combination of a variety of techniques including an exercise program, stretching, massage, and traction. As patients look for pain relief beyond traditional medicine, complementary and alternative medicine (CAM) treatments are increasingly being used for pain management [76, 77]. CAM interventions fall under a wide range of disciplines and include acupuncture, supplements and vitamins, biofeedback, massage, and hypnosis [76]. At this time, there are few studies demonstrating the efficacy of most CAM

interventions, with the exception of acupuncture. Studies of acupuncture show benefit across pain conditions, but the benefits appear to be short term [78].

Medical Cannabis for Chronic Pain: The Good, the Bad, and the Unknown

As alternatives to opioids are being debated, interest in cannabis for pain management and as an opioid-sparing alternative is growing. Currently, 29 US states have legalized the use of cannabis for medical purposes, with 9 states also allowing legal access to recreational cannabis. Cannabis use is considered medical when it is used to treat a specific disease or alleviate symptoms. Data from a large cohort of medical cannabis patients found that 87% report seeking their medical certification for moderate or severe pain, and even among nonmedical users, pain motives are often cited [79, 80]. As more states legalize medical cannabis, rates of cannabis use for chronic pain will only continue to increase. It follows that physicians who treat chronic pain need to be in a position to educate their patients about the potential risks and benefits of medical cannabis. Anecdotally some chronic pain patients report benefits from medical cannabis, and recent reviews suggest there is moderate quality evidence to support cannabis use for medical purposes, including some types of chronic pain (e.g., neuropathic pain) [81]. The National Academies of Sciences, Engineering, and Medicine released a report in 2017 that concluded there is "substantial evidence" for benefits of cannabis for chronic pain. However, a more recent review concluded that the efficacy data on cannabis for use in chronic pain is limited, and existing studies suffer from methodological limitations that make it difficult to draw definitive conclusions [82].

Given the risks associated with long-term opioid use, cannabis is being discussed as a potentially appealing alternative. In support of the "harm reduction" argument, several studies reported a reduction in opioid-related overdoses and deaths in states where cannabis is legal. Additionally, cross-sectional studies have found that patients report using less opioids after starting medical cannabis [83, 84]. However, it is risky to draw strong conclusions from ecological studies, such as those reporting links between state policy changes and opioid-related outcomes, and there is a dearth of longitudinal data, making it difficult to assess causality. A recent 4-year prospective study on nonmedical cannabis use among chronic pain patients prescribed with opioids found no evidence that cannabis use reduced opioid use [85]. This study does have limitations including the population studied (illicit cannabis use). An ongoing prospective cohort study in the United States is examining pain and opioid use outcomes among people using medical cannabis, which may offer further data [86].

Given the current state of the literature and lack of well-designed clinical trials, the verdict is still out as to whether cannabis will be a good treatment option for chronic pain. Because we do not yet know the long-term implications of using medical cannabis, providers and patients should proceed with caution until there have been large, well-designed clinical trials. The general recommendations to proceed

with caution are likely particularly relevant to subgroups of patients with known substance use disorders given the fact that having one type of substance use disorder can increase the risk for cannabis use disorder [87].

More broadly, the story of how the opioid epidemic unfolded – where the potential benefits of the substance were oversold and the consequences were underestimated – argues for a cautious approach when interpreting the early results of the research on cannabis for pain relief and underscores the importance of considering unintended consequences of broader use of cannabis for pain.

Managing Chronic Pain in Those with Substance Use Disorders and Chronic Pain

Although daily practice requires treatment providers who prescribe opioids to differentiate between those who are merely seeking medications for nonmedical use and those who have legitimate pain-related needs, it is clear that these are overlapping groups – with many individuals experiencing both pain and opioid use disorder [88]. Thus, efforts to expand treatments for chronic pain should not exclude those individuals who report medication misuse or symptoms of a substance use disorder. This extends to settings, such as addiction treatment programs, that likely see large numbers of patients with both pain and substance use disorders [89]. Research in this area is still emerging, in large part, because many prior studies of pain interventions excluded individuals with active or past substance use disorders. However, a recent study was conducted on Veterans receiving treatment for a mixture of substance use disorders, which included but was not limited to OUDs, who also reported chronic pain [90]. This study found that receipt of a psychosocial intervention that included content from both CBT and ACT was associated with greater improvements in self-reported pain levels and daily functioning as well as fewer days of alcohol use over a 1-year follow-up interval compared to an attention placebo group. These findings require replication, but they do hint at the potential benefits of addressing co-occurring pain and substance use disorders as a way to improve outcomes in both domains. Future work in this area should specifically target chronic pain in those with OUDs, where pain is particularly common. In addition, buprenorphine has been suggested as a possible therapeutic option for individuals with chronic pain and either opioid use disorder or what has been termed "complex persistent dependence," when a patient may not meet criteria for OUD but seems to have maladaptive use of opioid pain relievers [91, 92].

Summary and Conclusions

The story of the rise of the opioid epidemic in the United States has been told in multiple academic and nonacademic settings [1]. As reviewed previously, an increase in opioid prescribing was associated with a substantial rise in opioid-related adverse outcomes [2]. Recent data indicate that this story continues to evolve

[3]. Nonprescription opioids (e.g., heroin and fentanyl) are increasingly present in opioid overdoses, and the United States may have reached a "high water mark" in terms of the use of prescription opioids, with recent reports indicating that slightly fewer prescriptions are being written for opioids over the past 2–3 years [93]. These decreases likely reflect the use of new policies to discourage high-dose opioid prescribing at the state and health system level. A recent study in the Department of Veterans Affairs indicates that one of these newer approaches, referred to as the Opioid Safety Initiative, likely led to an acceleration of the ongoing shifts away from high-dose opioid prescribing in the VA [94]. Further studies are needed to determine the impact of other similar initiatives.

However, even as policy research continues, it is likely that the downward trend in opioid prescribing in the United States will continue for the foreseeable future. As the disincentives increase for treatment providers to use opioids, it is important to avoid creating "pain refugees" or patients who are in need of effective pain care, which may include a continuation of opioids, but are unable to receive pain treatment because of fears on the part of providers about sanctions related to the use of opioids for chronic pain. For those patients already receiving opioids who might benefit from a reduced dosage or discontinuation, it is essential that the process of tapering be done in a thoughtful and compassionate manner which includes shared decision-making with the patient. A recent pilot study demonstrated that a substantial percentage of patients receiving chronic pain therapy from a pain clinic were open to participating in an opioid taper and participation in a structured tapering process, which was combined with psychoeducation about pain and opioids, was not associated in any increases in pain or poorer functioning from the baseline period when these individuals were receiving higher opioid doses [95]. However, there is no evidence to support arbitrary or involuntary tapers, which risk causing withdrawal, pushing individuals into the street opioid market, or even to suicide. Similar studies are need to help treatment providers and patients understand the process of tapering and to develop strategies to help patients who may be appropriate for reduced opioid dosage to navigate a taper successfully without a corresponding increase in pain and decrease in quality of life.

More broadly, societal and health system-level solutions to the opioid crisis need to acknowledge the legitimate suffering of the millions of patients in this country with chronic pain. A sizeable portion of these individuals may also suffer from a substance use disorder – but those with and without a substance use disorder deserve effective pain care. It is unlikely that any single class of medication will be able to address the complicated physical and psychological needs of those with long-standing pain, and it is important to expand access to nonpharmacological treatments for these patients. Given that millions of these patients have already been provided with opioids and opioids will continue to be a part of pain care for the foreseeable future, these pain treatments will need to be made available to those with varying degrees of opioid exposure. Treatment providers need to understand the possibility for addiction in those receiving opioids but also understand the difference between physiological dependence and addiction. A comprehensive and optimally effective approach to pain care needs to provide patients with all levels of

opioid exposure/dependence with compassionate and comprehensive pain care. When patients have co-occurring pain and a substance use disorder, treatment should attempt to effectively address both of these conditions.

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