Uploaded to the VFC Website

2020

This Document has been provided to you courtesy of Veterans-For-Change!

Feel free to pass to any veteran who might be able to use this information!

For thousands more files like this and hundreds of links to useful information, and hundreds of "Frequently Asked Questions, please go to:

Veterans-For-Change

If Veterans don't help Veterans, who will?

Note: VFC is not liable for source information in this document, it is merely provided as a courtesy to our members & subscribers.

MEDICATIONS FOR OPIOID USE DISORDER SAVE LIVES

Committee on Medication-Assisted Treatment for Opioid Use Disorder

Alan I. Leshner and Michelle Mancher, *Editors*

Board on Health Sciences Policy

Health and Medicine Division

A Consensus Study Report of

The National Academies of

SCIENCES • ENGINEERING • MEDICINE

THE NATIONAL ACADEMIES PRESS

Washington, DC

www.nap.edu

THE NATIONAL ACADEMIES PRESS 500 Fifth Street, NW Washington, DC 20001

This activity was supported by a contract between the National Academy of Sciences and the National Institutes of Health (HHSN263201800029I/HHSN26300005) and the Substance Abuse and Mental Health Services Administration. Any opinions, findings, conclusions, or recommendations expressed in this publication do not necessarily reflect the views of any organization or agency that provided support for the project.

International Standard Book Number-13: 978-0-309-48648-4
International Standard Book Number-10: 0-309-48648-3
Digital Object Identifier: https://doi.org/10.17226/25310
Library of Congress Control Number: 2019939384

Additional copies of this publication are available from the National Academies Press, 500 Fifth Street, NW, Keck 360, Washington, DC 20001; (800) 624-6242 or (202) 334-3313; http://www.nap.edu.

Printed in the United States of America

Suggested citation: National Academies of Sciences, Engineering, and Medicine. 2019. *Medications for opioid use disorder save lives*. Washington, DC: The National Academies Press. doi: https://doi.org/10.17226/25310.

The National Academies of
SCIENCES • ENGINEERING • MEDICINE

The **National Academy of Sciences** was established in 1863 by an Act of Congress, signed by President Lincoln, as a private, nongovernmental institution to advise the nation on issues related to science and technology. Members are elected by their peers for outstanding contributions to research. Dr. Marcia McNutt is president.

The **National Academy of Engineering** was established in 1964 under the charter of the National Academy of Sciences to bring the practices of engineering to advising the nation. Members are elected by their peers for extraordinary contributions to engineering. Dr. C. D. Mote, Jr., is president.

The **National Academy of Medicine** (formerly the Institute of Medicine) was established in 1970 under the charter of the National Academy of Sciences to advise the nation on medical and health issues. Members are elected by their peers for distinguished contributions to medicine and health. Dr. Victor J. Dzau is president.

The three Academies work together as the **National Academies of Sciences, Engineering, and Medicine** to provide independent, objective analysis and advice to the nation and conduct other activities to solve complex problems and inform public policy decisions. The National Academies also encourage education and research, recognize outstanding contributions to knowledge, and increase public understanding in matters of science, engineering, and medicine.

Learn more about the National Academies of Sciences, Engineering, and Medicine at **www.nationalacademies.org**.

The National Academies of
SCIENCES • ENGINEERING • MEDICINE

Consensus Study Reports published by the National Academies of Sciences, Engineering, and Medicine document the evidence-based consensus on the study's statement of task by an authoring committee of experts. Reports typically include findings, conclusions, and recommendations based on information gathered by the committee and the committee's deliberations. Each report has been subjected to a rigorous and independent peer-review process and it represents the position of the National Academies on the statement of task.

Proceedings published by the National Academies of Sciences, Engineering, and Medicine chronicle the presentations and discussions at a workshop, symposium, or other event convened by the National Academies. The statements and opinions contained in proceedings are those of the participants and are not endorsed by other participants, the planning committee, or the National Academies.

For information about other products and activities of the National Academies, please visit www.nationalacademies.org/about/whatwedo.

COMMITTEE ON MEDICATION-ASSISTED TREATMENT FOR OPIOID USE DISORDER

ALAN I. LESHNER (*Chair*), Chief Executive Officer Emeritus, American Association for the Advancement of Science
HUDA AKIL, Co-Director and Research Professor, Molecular & Behavioral Neuroscience Institute; Distinguished University Professor and Quarton Professor of Neurosciences, Department of Psychiatry, University of Michigan
COLLEEN BARRY, Fred & Julie Soper Professor and Chair, Department of Health Policy and Management, Johns Hopkins Bloomberg School of Public Health
KATHLEEN CARROLL, Albert E. Kent Professor of Psychiatry, Yale School of Medicine
CHINAZO CUNNINGHAM, Professor, Albert Einstein College of Medicine, Montefiore Medical Center
WALTER GINTER, Project Director, Medication Assisted Recovery Support Project
TRACI GREEN, Associate Professor, Emergency Medicine; Associate Director and Senior Scientist, Injury Prevention Research Center, Boston University/Boston Medical Center
YASMIN HURD, Ward Coleman Chair of Translational Neuroscience; Director, Addiction Institute at Mount Sinai, Icahn School of Medicine at Mount Sinai
ALAN JETTE, Professor, MGH Institute of Health Professions
LAURA R. LANDER, Associate Professor and Addiction Therapist, Department of Behavioral Medicine and Psychiatry and Department of Neuroscience, West Virginia University
DAVID PATTERSON SILVER WOLF, Associate Professor, Washington University
SEUN ROSS, Director, Nursing Practice and Work Environment, American Nurses Association
SCOTT STEIGER, Associate Clinical Professor of Medicine and Psychiatry, University of California, San Francisco
DAVID VLAHOV, Associate Dean for Research and Professor, Yale School of Nursing

Study Staff

MICHELLE MANCHER, Study Director
CLARE STROUD, Senior Program Officer
EMILY BUSTA, Associate Program Officer (*until September 2018*)

BENJAMIN KAHN, Associate Program Officer
DANIEL FLYNN, Research Associate (*until December 2018*)
MEREDITH HACKMANN, Research Associate (*until December 2018*)
MICHAEL BERRIOS, Senior Program Assistant
MARIAM SHELTON, Board on Health Sciences Policy Program Coordinator
DANIEL BEARSS, Research Librarian
ANDREW M. POPE, Director, Board on Health Sciences Policy

Consultant

ANNA NICHOLSON, Science Writer

Reviewers

This Consensus Study Report was reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise. The purpose of this independent review is to provide candid and critical comments that will assist the National Academies of Sciences, Engineering, and Medicine in making each published report as sound as possible and to ensure that it meets the institutional standards for quality, objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process.

We thank the following individuals for their review of this report:

JAN M. BROWN, SpiritWorks Foundation Center for the Soul
H. WESTLEY CLARK, Santa Clara University
KELLY J. CLARK, American Society of Addiction Medicine
BRANDEE IZQUIERDO, SAFE Project
CHRISTOPHER M. JONES, U.S. Centers for Disease Control and Prevention
PAULA J. LUM, University of California, San Francisco
SANDRA A. SPRINGER, Yale School of Medicine
JOYCELYN SUE WOODS, National Alliance for Medication Assisted Recovery

Although the reviewers listed above provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations of this report, nor did they see the final draft before its release. The review of this report was overseen by **JOHN H. KRYSTAL,** Yale

School of Medicine, and **KRISTINE GEBBIE,** Flinders University School of Nursing and Midwifery. They were responsible for making certain that an independent examination of this report was carried out in accordance with the standards of the National Academies and that all review comments were carefully considered. Responsibility for the final content rests entirely with the authoring committee and the National Academies.

Preface

The United States is experiencing a public health crisis of almost unprecedented scale: an epidemic of opioid use disorder (OUD) and related overdose deaths. It is not wholly new, as opioid addiction and the resulting societal disruption have been major problems in many countries for hundreds of years, but its magnitude has increased exponentially in the past decades.

As this Consensus Study Report articulates, modern medicine and the science that underpins it have developed and provided a set of highly effective tools that can help address the opioid epidemic—specifically, three U.S. Food and Drug Administration–approved medications—that have been severely underused, even in the health care sector. Their effectiveness and why they are not more widely used are the subjects of this report. Most of the factors impeding their full use can and must be dealt with if real progress is to be made. These factors include the misunderstandings and stigma surrounding both addiction and the medications used to treat it, as well as counterproductive ideologies that consider addiction simply a failure of will or a moral weakness, as opposed to understanding OUD as a chronic disease of the brain that requires medical treatment. This misunderstanding and stigma must be addressed; they have resulted in hundreds of thousands of patients being denied access to life-saving medications on non-medical, non-scientific grounds, which our committee considers to be unethical.

As with all such studies, the committee developed its conclusions based on a review of the scientific literature as it stands at the point in time of the committee's work. Fortunately, there is a robust research enterprise that is continuing to work on OUD and its treatment. We are confident that these

efforts will yield results that will continue to increase understanding of OUD and the most effective ways to prevent and treat it. Knowledge needs include refining in detail the most effective protocols for administering medications to specific individuals and subpopulations and the identification of additional molecular targets and approaches to enable the development of new and even more effective medications. Other research needs are discussed throughout the report.

The committee would like to express its great appreciation to the study director, Michelle Mancher, and her colleagues on the National Academies staff whose dedication, competence, and hard work have greatly improved the quality of this report. We also greatly appreciate the insight and support of our sponsors, the National Institute on Drug Abuse of the National Institutes of Health and the Substance Abuse and Mental Health Services Administration.

Alan I. Leshner, *Chair*
Committee on Medication-Assisted
Treatment for Opioid Use Disorder

Contents

APPENDIXES

Boxes and Figures

BOXES

FIGURES

Acronyms and Abbreviations

AAP	American Academy of Pediatrics
ACA	Patient Protection and Affordable Care Act
CARA	Comprehensive Addiction and Recovery Act
CBD	cannabidiol
CDC	U.S. Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CHC	community health center
DATA	Drug Addiction Treatment Act
DEA	Drug Enforcement Administration
EHR	electronic health record
FDA	U.S. Food and Drug Administration
HCV	hepatitis C virus
HIV	human immunodeficiency virus
MAT	medication-assisted treatment
MHPA	Mental Health Parity Act
NP	nurse practitioner
NSDUH	National Survey on Drug Use and Health

OTP	opioid treatment program
OUD	opioid use disorder
PA	physician assistant
PDMP	Prescription Drug Monitoring Program
QTc	corrected QT interval
SAMHSA	Substance Abuse and Mental Health Services Administration
siOAT	supervised injectable opioid agonist treatment
SROM	slow-release oral morphine
SUD	substance use disorder
THC	tetrahydrocannabinol

Summary[1]

The opioid crisis in the United States has come about because of excessive use of these drugs for both legal and illicit purposes and unprecedented levels of consequent opioid use disorder (OUD). More than 2 million people in the United States are estimated to have OUD, which is caused by prolonged use of prescription opioids, heroin, or other illicit opioids. OUD is a life-threatening condition associated with a 20-fold greater risk of early death due to overdose, infectious diseases, trauma, and suicide. Mortality related to OUD continues to escalate as this public health crisis gains momentum across the country, with opioid overdoses killing more than 47,000 people in 2017 in the United States. Efforts to date have made no real headway in stemming this crisis, in large part because tools that already exist—like evidence-based medications—are not being deployed to maximum impact. To support the dissemination of accurate, patient-focused information about evidence-based treatment for OUD, the National Institute on Drug Abuse and the Substance Abuse and Mental Health Services Administration asked a committee convened by the National Academies of Sciences, Engineering, and Medicine to examine the evidence base for medications to treat OUD and to identify barriers that prevent people from accessing safe, effective, medication-based treatment (see Box S-1). The full Statement of Task to the committee is provided in Box S-3 at the end of this summary.

[1] This summary does not include references. Citations for the discussion presented in this summary appear in subsequent chapters.

BOX S-1
Medication-Based Treatment for Opioid Use Disorder

Although medication-assisted treatment (MAT) is a term commonly used to describe treatment programs for opioid use disorder (OUD) that include any of the three opioid agonist or antagonist medications, the committee chose to use the term "medication-based treatment for OUD" rather than MAT throughout this report. This change in nomenclature aligns with the committee's conceptual framework of OUD as a chronic disorder for which medications are first-line treatments that are often an integral part of a person's long-term treatment plan, rather than complementary or temporary aids on the path to recovery.

OUD is a chronic brain disease that comes about because of the effects of prolonged opioid use on brain structure and function. These brain changes—and the resulting addiction—can be treated with life-saving medications, but those medications are not available to most of the people who need them. Methadone, buprenorphine, and extended-release naltrexone are safe and highly effective medications that are already approved by the U.S. Food and Drug Administration (FDA) to treat OUD. By alleviating withdrawal symptoms, reducing opioid cravings, or decreasing the response to future drug use, these medications[2] make people with OUD less likely to return to drug use and risk a fatal overdose. These medications also help people restore their functionality, improve their quality of life, and reintegrate into their families and communities. These medications save lives, but the majority of people with OUD in the United States receive no treatment at all.

As with any other disease, medications should not be withheld from people with OUD without sufficient medical justification. Withholding them on ideological or other non-evidence-based grounds is denying people needed medical care. However, some addiction treatment facilities that ban medications are still being supported by funding streams that are tied to the criminal justice system or housing authorities, creating strong incentives to steer patients toward non-medication-based treatment approaches.

As the number of people with OUD surges, the need for treatment is far outstripping the current capacity to deliver it. A host of systemic barriers prevent people from accessing those medications. For example, when OUD treatment delivery settings are separate from the rest of medical care, the surrounding regulatory and legal requirements can impose hard-to-

[2] Only methadone and buprenorphine alleviate withdrawal symptoms; all three medications decrease craving and block the euphoric effects of taking other opioids.

overcome barriers on accessing medication-based treatment for OUD. The current system of care delivery for OUD is fragmented and inequitable, so a coordinated response will be required to overcome the inertia that has allowed the crisis to spiral to this extent. Box S-2 summarizes the major conclusions of the report. Curbing the epidemic will require an "all hands on deck" strategy across every sector—health care, criminal justice, patients and their family members, and beyond—because no sector alone will be able to resolve the crisis. Making access to medications much broader and more equitable is a high priority for making meaningful progress in saving lives of those with OUD.

OPIOID USE DISORDER IS A TREATABLE CHRONIC BRAIN DISEASE

Addiction is a chronic disease that involves compulsive or uncontrolled use of one or more substances in the face of negative consequences. As with other chronic medical conditions, a confluence of genetic, environmental, and social factors shape a person's vulnerability to addiction and ease of recovery from it. These factors determine a person's propensity to start using drugs and to keep using them, as well as a person's susceptibility to the particular types of neurobiological changes in the brain that characterize the progression to addiction. Building on decades of research, the scientific

BOX S-2
Summary of Conclusions

1. Opioid use disorder is a treatable chronic brain disease.
2. U.S. Food and Drug Administration (FDA)-approved medications to treat opioid use disorder are effective and save lives.
3. Long-term retention on medications to treat opioid use disorder is associated with improved outcomes.
4. A lack of availability of behavioral interventions is not a sufficient justification to withhold medications to treat opioid use disorder.
5. Most people who could benefit from medication-based treatment for opioid use disorder do not receive it, and access is inequitable across subgroups of the population.
6. Medication-based treatment is effective across all treatment settings studied to date. Withholding or failing to have available all classes of FDA-approved medication for the treatment of opioid use disorder in any care or criminal justice setting is denying appropriate medical treatment.
7. Confronting the major barriers to the use of medications to treat opioid use disorder is critical to addressing the opioid crisis.

community has coalesced around the brain disease model of addiction. In people with OUD and other substance use disorders (SUDs), prolonged and repeated drug use over time causes lasting effects on brain structure and function. Prescription and illicit opioids produce powerful and sustained effects on the brain's opioid system; repeated use can disrupt the regulation of the system and result in tolerance, physical dependence, and addiction. The evidence shows that these brain changes can be treated effectively with medications that help people refrain from using drugs, thus sharply reducing their risks of overdose and death. By alleviating opioid cravings and withdrawal symptoms, the medications can also provide opportunities to address the behavioral and social components of addiction, which are critically important both to the disorder's development and its treatment.

This scientific understanding of OUD is at odds with the prevailing public perception of the disorder, which is colored by the misconception of addiction as simply a moral failing. That popular view has proliferated through generations of social stigmatization directed at people who use drugs; this misinformed stigma has also spread to the medications used to treat OUD. In fact, people with OUD have a chronic disease that, like many others, warrants long-term medical management beyond episodic acute care incidents.

Conclusion 1: Opioid use disorder is a treatable chronic brain disease.

OUD is a treatable chronic brain disease resulting from the changes in neural structure and function that are caused over time by repeated opioid use. The behavioral and social contexts are critically important to both its development and treatment. Stopping opioid misuse is extremely difficult. Medications are intended to normalize brain structure and function.

MEDICATIONS FOR OPIOID USE DISORDER SAVE LIVES

OUD is caused by changes in brain circuitry that can be treated with medication to restore healthy brain function, which leads to improvements in behaviors associated with addiction. The medications currently approved by FDA for treating OUD are evidence based, safe, and highly effective. Medication-based treatment for OUD focuses first on managing withdrawal symptoms and then on controlling or eliminating the patient's compulsive opioid use, most commonly with the agonist medications methadone or buprenorphine. Large systematic reviews and randomized controlled trials show that patients with OUD who receive these medications are less likely to die from overdose or other causes related to their addiction. Patients who receive medication have higher treatment retention rates, better long-term treatment outcomes, and improved social functioning; they are also less likely to inject drugs or transmit infectious diseases. For patients who have gone through withdrawal from opioids for a sufficient time, extended-release naltrexone may be used for maintenance treatment. Available evidence clearly supports the use of medications and the need to expand access to medications to reduce or eliminate compulsive opioid use, to reduce the risk of premature death, and to improve the quality of life of people with OUD and their families.

Methadone, buprenorphine, and extended-release naltrexone all work by targeting the mu-opioid receptor within the opioid system. Because each medication has a distinct mechanism of action, the most appropriate medication and dosage vary across patients and may vary in the same patient over the course of treatment. The existing medications are very effective, but they are not perfect; for example, evidence gaps remain about how to choose the most effective medication for a particular patient and how best to retain people in treatment, which is itself a significant problem. Moreover, because OUD has complex behavioral and social causes and consequences, it is not yet known which behavioral interventions might be most appropriate to help restore patients to full functionality. Therefore, even though there is a need to act urgently to improve access to existing medications, innovation cannot stagnate. Research should continue to focus on developing new and better medications to treat OUD, on determining the most effective behavioral therapies to maximize outcomes, and on refining the most appropriate protocols for their effective use.

Conclusion 2: U.S. Food and Drug Administration–approved medications to treat opioid use disorder are effective and save lives.

FDA-approved medications to treat OUD—methadone, buprenorphine, and extended-release naltrexone—are effective and save lives. The most appropriate medication varies by individual and may change over time. To stem the opioid crisis, it is critical for all FDA-approved options to be available for all people with OUD. At the same time, as with all medical disorders, continued research is needed on new medications, approaches, and formulations that will expand the options for patients.

Evidence demonstrates that patients who receive longer-term treatment with medication for OUD have better treatment outcomes; they are also less likely to die from overdose if they return to use while on medication. In fact, people with OUD are up to 50 percent less likely to die when they are being treated long term with methadone or buprenorphine. Further research is needed to define an optimal treatment regimen for each of the available medications and to directly compare the effects of the three medications' long-term use. Nonetheless, in spite of the need for more research, the body of evidence amassed over the past 50 years underscores the benefits of long-term retention on medication.

Conclusion 3: Long-term retention on medication to treat opioid use disorder is associated with improved outcomes.

There is evidence that retention on medication for the long term is associated with improved outcomes and that discontinuing medication often leads to relapse and overdose. There is insufficient evidence regarding how the medications compare over the long term.

Treatment with a combination of medication and evidence-based behavioral interventions (e.g., contingency management approaches, cognitive behavioral therapy, and structured family therapy) can be effective for many people with OUD. However, little is known about which combinations of medication and behavioral interventions are most effective, which patients are most likely to benefit from behavioral interventions, and which patients may do well with medications and appropriate medical management alone. Even among patients who would benefit from the addition of behavioral interventions, it is better for them to receive medication with appropriate medical management than to have it withheld. The life-saving aspects of these medications have been established even in the absence of accompanying behavioral interventions. Given the resource limitations faced in many settings, it is critical that providers do not withhold medications from their patients just because behavioral interventions are not available.

Conclusion 4:
A lack of availability or utilization of behavioral interventions is not a sufficient justification to withhold medications to treat opioid use disorder.

Behavioral interventions, in addition to medical management, do not appear to be a necessary part of treatment in all cases. Some people may do well with medication and medical management alone. However, evidence-based behavioral interventions can be useful in engaging people with OUD in treatment, retaining them in treatment, improving their outcomes, and helping them resume a healthy functioning life. There is inadequate evidence about which behavioral interventions, when used in conjunction with medications for OUD, are most helpful for which patients, including evidence on how effective peer support is; more research is needed to address this knowledge deficit.

MEDICATIONS ARE NOT AVAILABLE TO MANY PEOPLE WHO NEED THEM

Most people with OUD in the United States do not receive any treatment at all, and those who do receive any type of treatment may wait years to do so. Of the small proportion of people who do receive treatment, just a fraction receive medication. Access to evidence-based treatment is poor across the board, but it is starkly inequitable among certain generational, racial, ethnic, social, and economic groups. Although the research is not yet

granular enough to develop tailored treatment guidelines for specific subpopulations, the available evidence supports the effectiveness of medication for treating OUD in all groups, including adolescents, pregnant women, and people with comorbidities. However, the treatment gap is exacerbated for vulnerable populations, whose members face steep barriers in accessing medications.

Conclusion 5:
Most people who could benefit from medication-based treatment for opioid use disorder do not receive it, and access is inequitable across subgroups of the population.

Available evidence suggests that medication-based treatment for OUD is highly effective across all subgroups of the population, including adolescents, older persons, pregnant women, individuals with co-occurring disorders (e.g., psychiatric disorders, SUDs, infectious diseases), and all racial, sex and gender, and socioeconomic groups. However, the nature and extent of OUD in these groups appear to vary greatly, as does access to needed medications. To more widely and equitably address the opioid crisis, additional study will be required of the significance and causes of these differences as well as of the potential need for specific medication-based treatment guidelines for subpopulations.

Access to medications for OUD remains inequitable across different treatment settings as well. In the United States, methadone can only be administered through specialty facilities known as opioid treatment programs (OTPs), even though the available evidence shows that delivering it through an office-based medical practice setting is also effective. Moreover, most residential treatment facilities do not offer medications, and if they do, they rarely offer all three medications.

Despite the large and increasing numbers of people with OUD entering the criminal justice system in the United States, evidence-based medications are often withheld or are only provided on a limited basis for medically supervised withdrawal. As a result, few people with OUD receive medication while incarcerated or under the supervision of drug courts. In addition, justice-involved people who do receive medication for OUD are often not linked with care upon release, leading to treatment discontinuation and the concomitant risks of overdose and death. Given that these medications are known to save lives, it is arguable that withholding them from persons with OUD is unethical, as withholding insulin or blood pressure medications would be.

Pharmacies, mobile medication units, community health centers, emergency departments, and other care settings provide opportunities to engage people with OUD and link them to evidence-based care. Expanding medications for OUD into a broader range of care settings would save lives and build the capacity to make real progress against the epidemic.

Conclusion 6:
Medication-based treatment is effective across all treatment settings studied to date. Withholding or failing to have available all U.S. Food and Drug Administration–approved classes of medication for the treatment of opioid use disorder in any care or criminal justice setting is denying appropriate medical treatment.

Treatment with FDA-approved medications is clearly effective in a broader range of care settings (e.g., office-based care setting, acute care, and criminal justice settings) than is currently the norm. There is no scientific evidence that justifies withholding medications from OUD patients in any setting or denying social services (e.g., housing, income supports) to individuals on medication for OUD. Therefore, to withhold treatment or deny services under these circumstances is unethical.

A number of barriers, both social and systemic, prevent people with OUD from accessing the life-saving medications they need. Making headway against the opioid crisis will require addressing barriers related to stigma and discrimination, inadequate professional education, overly stringent regulatory and legal policies, and the fragmented systems of care delivery and financing for OUD.

The stigmatization of people with OUD is a major barrier to treatment seeking and retention. Social stigma from the general public is largely

rooted in the misconception that addiction is simply the result of moral failing or a lack of self-discipline that is worthy of blame, rather than a chronic brain disease that requires medical treatment. Evidence demonstrates that social stigma contributes to public acceptance of discriminatory measures against people with OUD and to the public's willingness to accept more punitive and less evidence-based policies for confronting the epidemic. Patients with OUD also report stigmatizing attitudes from some professionals within and beyond the health sector, further undercutting access to evidence-based treatment. The medications, particularly the agonist medications, used to treat OUD are also stigmatized. This can manifest in providers' unwillingness to prescribe medications due to concerns about misuse and diversion and in the public's mistaken belief that taking medication is "just substituting one drug for another." Importantly, the rate of diversion is lower than for other prescribed medications, and it declines as the availability of medications to treat OUD increases.

Despite the mounting crisis, the health care workforce in the United States does not receive adequate, standardized education about OUD and the evidence base for medication-based treatment. This has created a shortage of providers who are knowledgeable, confident, and willing to provide medications to patients. Many rural areas are being overwhelmed by the opioid epidemic and have very few, if any, trained and licensed providers who can prescribe the medications. Misinformation and a lack of knowledge about OUD and its medications are also prevalent across the law enforcement and criminal justice systems.

Stringent laws and regulatory policies pose substantial barriers to methadone and buprenorphine access. Laws and regulatory requirements restrict outpatient methadone treatment to state- and federally certified OTPs, which is detrimental to long-term treatment adherence for many patients. Unlike methadone, buprenorphine is approved to be prescribed in office-based settings, but only by providers who undergo specialized training and obtain a waiver from the Drug Enforcement Administration. Few providers in the United States have such waivers (estimated at less than 3 percent), and additional regulations limit the number of patients that each provider can treat with medication. To compound the problem, most waivered providers prescribe buprenorphine at well below the capacity they are allowed. These policies are not supported by evidence, nor are such strict regulations imposed on access to life-saving medications for other chronic diseases.

The system of care delivery for OUD is fragmented and poorly integrated into the broader health system in the United States. Treatment settings and financing streams for SUDs are generally detached from primary care, further obstructing access to medications for OUD, especially among people with other co-occurring conditions. Many providers are reluctant to treat people with OUD because they do not receive timely and sufficient reimbursement by public and private insurance coverage, which often limits

or excludes evidence-based medication treatment services for OUD. These barriers are compounded by other restrictions, such as prior authorization policies, dose limitations or forced dose tapers, counseling requirements, and annual or lifetime limits on the amount of OUD medication a person can receive. Almost half of nonelderly adults with OUD are covered by Medicaid, which has been shown to help connect people with medication-based treatment for OUD and to improve treatment retention. However, Medicaid coverage for OUD medications varies widely by state, with some states excluding methadone and buprenorphine entirely.

Conclusion 7: Confronting the major barriers to the use of medications to treat opioid use disorder is critical to addressing the opioid crisis.

The major barriers to the use of medications for OUD include

- High levels of misunderstanding and stigma toward drug addiction, individuals with OUD, and the medications to treat it.
- Inadequate education of the professionals responsible for working with people with OUD, including treatment providers and law enforcement and other criminal justice personnel.
- Current regulations around methadone and buprenorphine, such as waiver policies, patient limits, restrictions on settings, and other policies that are not supported by evidence or employed for other medical disorders.
- The fragmented system of care for people with OUD and current financing and payment policies.

BOX S-3
Statement of Task

To support the dissemination of accurate patient-focused information about treatments for addiction, and to help provide scientific solutions to the current opioid crisis, an ad hoc committee under the auspices of the National Academies of Sciences, Engineering, and Medicine will conduct a study of the evidence base on medication-assisted treatment (MAT)[a] for opioid use disorder (OUD). Specifically, the committee will

- Review current knowledge and gaps in understanding regarding the effectiveness of MAT for treating OUD;
- Examine available evidence on the range of parameters and circumstances in which MAT can be effectively delivered (e.g., duration of treatment, populations, settings, and interventions to address social determinants of health as a component of MAT);
- Identify challenges in implementation and uptake; and
- Identify additional research needed on MAT for OUD.

Based on its review of the literature and input from the public workshop, the committee will develop a report with its findings and conclusions.

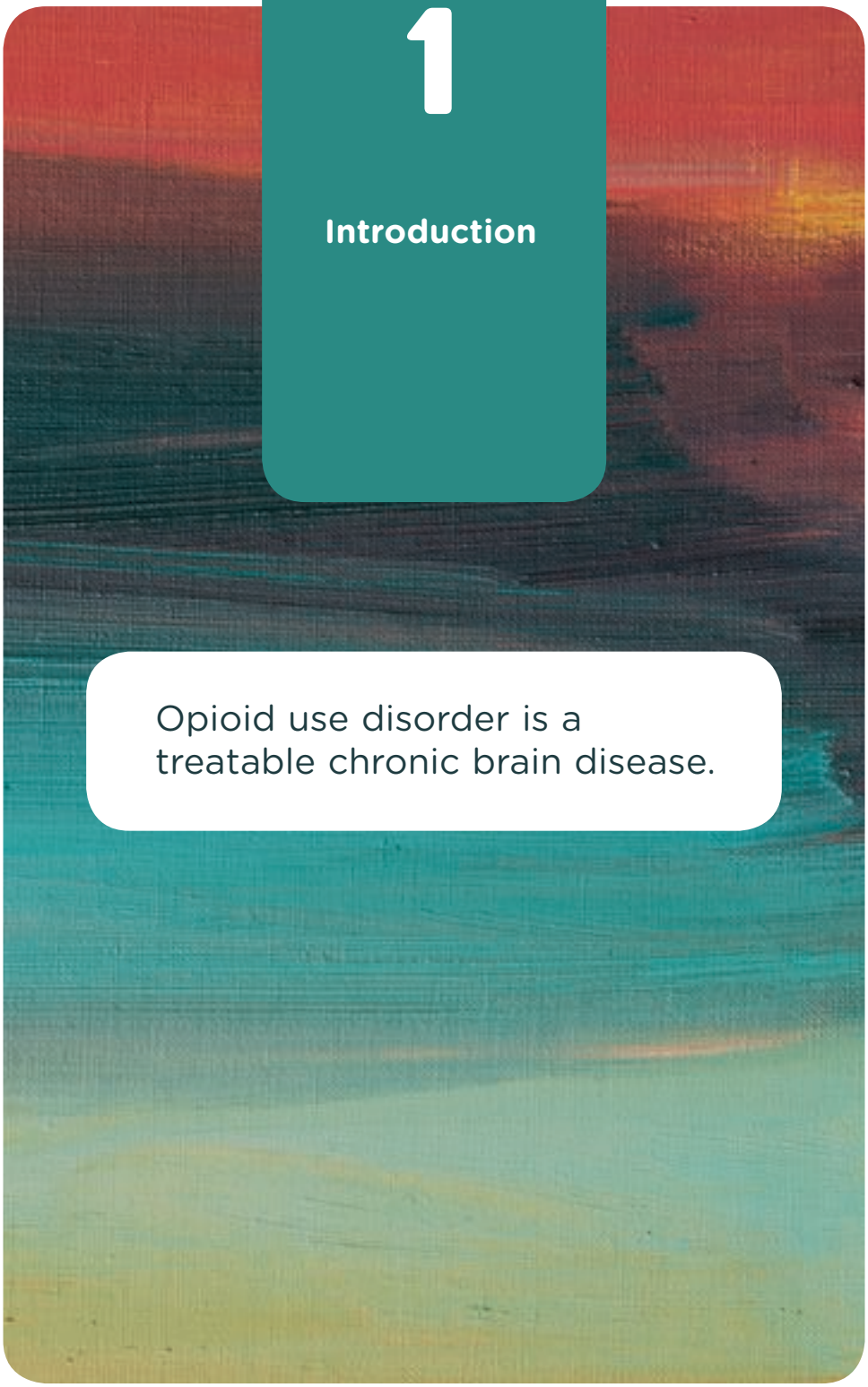
[a] See Box S-1 for an explanation of the committee's decision to not use the term MAT in this report.

STATEMENT OF TASK AND STUDY METHODOLOGY

This consensus study was carried out by the committee between October 2018 and March 2019. Study activities included a comprehensive literature review of the effectiveness of medications for OUD and the barriers people face in accessing them. The committee held a 1.5-day public workshop in Washington, DC, which was summarized in a Proceedings of a Workshop—in Brief, as well as two 2-day closed committee meetings. The Statement of Task to the committee is provided in Box S-3.

1

Introduction



Opioid use disorder is a treatable chronic brain disease.

The United States is facing an epidemic of opioid-related mortality and morbidity that is unparalleled in its scope and staggering in its impact. Drug overdoses are the leading cause of accidental deaths in the United States (Volkow et al., 2014). The U.S. Centers for Disease Control and Prevention (CDC) reports that more than 70,000 people in the United States died of drug overdoses in 2017 (Hedegaard et al., 2018), and the rise in drug overdoses has been linked to recent declines in American life expectancy (Joszt, 2018). Two-thirds (more than 47,000) of drug overdose deaths were caused by opioids—both legal and illicit (CDC, 2018b). Emergency departments had 358,000 visits from opioid poisoning in 2015 alone (Weiss and Heslin, 2018).

This public health crisis has emerged from two intertwined epidemics: the excessive use of opioids for both legal and illicit purposes, and unprecedented levels of consequent opioid use disorder (OUD). According to 2016 data from the National Survey on Drug Use and Health, more than 11.8 million people over age 12 had misused opioids within the prior 12 months, with 11.5 million people having misused prescription opioids (of an estimated 91.8 million adults who used prescription opioids), and 948,000 people had used heroin that year—including 641,000 people who used both types of opioids (Ahrnsbrak et al., 2017; Han et al., 2017). Among these, an estimated 2.1 million people suffered from an OUD, including 1.8 million with prescription OUD and 646,000 people with heroin use disorder, which are not mutually exclusive (Ahrnsbrak et al., 2017). People who misuse prescription opioids are almost 20 times more likely to use heroin for the first time, and, although just 4 to 6 percent of people who misuse prescription opioids transition to heroin within 5 years, 80 percent of people who use heroin have previously misused prescribed opioids (Carlson et al., 2016; Cicero et al., 2014a; Muhuri et al., 2013).

The current U.S. opioid epidemic began in the 1990s, when overprescribing of opioids for pain management[1] led to their extensive diversion and misuse (Axeen, 2018; Bohnert et al., 2011; Kolodny et al., 2015; Lyapustina and Alexander, 2015; Yang et al., 2018). Heroin overdoses began to escalate rapidly in 2010, followed by a wave of overdose deaths due to synthetic opioids that began in 2013 and continues to rise each year as the illicitly manufactured, synthetic opioid fentanyl floods street-drug markets (Seth et al., 2018). Together, overdoses of legally prescribed and illicit opioids killed almost 400,000 people in the United States between 1999 and 2017,

[1] Around two-thirds of people who misuse opioids report doing so for pain management; more than one-third of people who misuse opioids report obtaining them by prescription from a health care provider. Between 21 and 29 percent of people who are prescribed opioids for chronic pain will misuse them, and an estimated 8 to 12 percent of people who misuse them will develop an OUD (Vowles et al., 2015).

with the annual death toll increasing five-fold between the beginning and end of that period (CDC, 2018a). Synthetic-opioid overdose deaths increased by 45 percent between 2016 and 2017 (Hedegaard et al., 2018).

The impact of the opioid epidemic extends far beyond overdose mortality or the immediate consequences to individuals who use opioids or their families. There has been a re-emerging public health crisis of infectious diseases driven by the opioid epidemic, with the transmission of HIV and hepatitis C virus increasing with the rise in the numbers of young adults injecting drugs, which also increases susceptibility to endocarditis and infections of the skin, bones, and joints (CDC, 2017). Given the compounding risk factors of overdose, infectious diseases, trauma, and suicide, people with OUD have a 20-fold greater chance of early death (Schuckit, 2016). Women who use opioids while pregnant can give birth to newborns with neonatal abstinence syndrome; the number of cases of this syndrome increased by 500 percent between 2000 and 2012 in the United States (Ko et al., 2016; Patrick et al., 2015).

The socioeconomic consequences of the opioid epidemic are also proliferating in the form of health care costs, loss of productivity, and criminal involvement. CDC estimated that the economic burden of prescription opioid misuse in the United States is upward of $78 billion per year (Florence et al., 2016). The Council of Economic Advisers estimated the social cost of the opioid epidemic to be $504 billion in 2015 (Council of Economic Advisers, 2017). In addition, the OUD epidemic has been linked to an increase in the number of children in foster care (Radel et al., 2018) and linked to homelessness and housing insecurity (Doran et al., 2018).

Consensus is growing that the opioid epidemic needs to be addressed on multiple fronts by implementing evidence-based strategies to prevent OUD, to treat OUD successfully, and to manage pain effectively while mitigating the risks of addiction, misuse, and diversion (IOM, 2011; NASEM, 2017). The most common approaches for treating OUD in the United States can be divided into medication-based treatment programs (see Box 1-1) and non-medication-based models. This Consensus Study Report focuses on medication-based treatment for OUD; other treatment approaches were not reviewed in detail because that would have been outside the scope of the committee's task. However, the issue of whether behavioral interventions are required for medication to be effective is considered in other sections of this Consensus Study Report. Three medications are currently approved by the U.S. Food and Drug Administration (FDA) for the treatment of OUD: methadone, buprenorphine, and the long-acting form of naltrexone (see Box 1-2 for more information on the medications).

Treating OUD with medication is an evidence-based modality, in which medications are part of a comprehensive "whole patient" approach that may also involve behavioral counseling, community-based peer support,

BOX 1-1
Medication-Based Treatment for Opioid Use Disorder

Although medication-assisted treatment (MAT) is a term commonly used to describe treatment programs for opioid use disorder (OUD) that include any of the three opioid agonist or antagonist medications, the committee has chosen to use the term "medication-based treatment for OUD" rather than MAT throughout this report. This change in nomenclature aligns with the committee's conceptual framework of OUD as a chronic disorder for which medications are first-line treatments that are often an integral part of a person's long-term treatment plan, rather than complementary or temporary aids on the path to recovery.

primary care, and wrap-around services that support the long-term care of people with OUD. As part of an overall treatment strategy, the use of medications supports long-term remission. Medication is also a core component of medically supervised withdrawal from opioids, as it can alleviate acute withdrawal symptoms and reduce cravings. Each medication has its own treatment characteristics—and can affect individuals in different ways—so the treatment regimen needs to be tailored to patients' specific conditions and needs.

As presented in Chapter 2, the available evidence clearly establishes that a core element of successful treatment of OUD is medication that is administered appropriately—that is, with medical management that consists of regular provider meetings with ongoing monitoring of drug use and psychosocial functioning. Large systematic reviews and randomized controlled trials have demonstrated that treatment with either methadone or buprenorphine is associated with an array of positive outcomes, including fewer fatal overdose deaths (Schwartz et al., 2013), better treatment retention rates (Bart, 2012; Mattick et al., 2009, 2014; Schuckit, 2016), lower rates of other opioid use (Bart, 2012; Kakko et al., 2003; Mattick et al., 2009, 2014; Thomas et al., 2014), decreased mortality (Schuckit, 2016), less injection drug use (Woody et al., 2014), reduced transmission of HIV infections (Gowing et al., 2011), improved social functioning (Bart, 2012; Schuckit, 2016), decreased engagement in criminal activity (Schuckit, 2016), and lower rates of neonatal abstinence syndrome (Thomas et al., 2014). Expanding access to these medications reduces the number of deaths due to opioid overdose (Cicero et al., 2014b). Extended-release naltrexone is newer and has not been studied as extensively. However, the studies that have been done have consistently found that its administration demonstrates better retention in treatment, lower rates of opioid use, and lower rates of opioid craving than a placebo (Jarvis et al., 2018). Retention rates of individuals in

BOX 1-2
U.S. Food and Drug Administration–Approved Medications for the Treatment of Opioid Use Disorder

Methadone, buprenorphine, and extended-release naltrexone are currently approved by the U.S. Food and Drug Administration (FDA) for the treatment of opioid use disorder (OUD). Methadone and buprenorphine are known to be effective in relieving withdrawal symptoms during the acute phase of treatment (medically supervised withdrawal) and in reducing cravings and illicit opioid use when used for the long term (known as the maintenance phase). Naltrexone is only used as maintenance treatment.

As an opioid-agonist medication, methadone fully activates the brain's opioid receptors through the same mechanism as prescription or illicit opioids, but it is safer and less addictive because its uptake is slower and its effects less euphoric. Methadone is typically taken orally once daily and administered in person at opioid treatment programs. Long-term use of methadone is commonly referred to as methadone maintenance. When the term "methadone treatment" is used in this report, it refers to methadone maintenance treatment.

Buprenorphine is a partial opioid-agonist medication that activates opioid receptors. It is typically taken under the tongue and prescribed by a certified provider, without requiring the administration of the medication to be observed. It is available by injection, which lasts 28 days, or by implant, which lasts 6 months. The most commonly prescribed formulation contains naloxone as a deterrent to misuse, because it triggers withdrawal if injected. When the term "buprenorphine treatment" is used in this report, it may refer to any of the forms of buprenorphine.

Naltrexone is an opioid antagonist, and it works by blocking opioid receptors and eliminating the euphoric and pain-relieving effects of opioids. It can be administered by mouth daily or as depot injection once monthly, but the oral formulation has been shown to be ineffective for OUD. Only an extended-release formulation of naltrexone is approved by FDA for treatment of OUD. Unlike the other two medications, naltrexone treatment requires stopping the use of any opioids for a period of 7 to 10 days prior to treatment initiation, which can be extremely challenging for people with OUD.

SOURCES: Schuckit, 2016; Volkow et al., 2014, 2018.

medication-based treatment for OUD are generally low, but they vary widely across treatment settings (Timko et al., 2016).

Despite the preponderance of evidence that medications to treat OUD are safe and effective, they remain highly underused in the United States. In 2017, about 80 percent of people who needed OUD treatment did not receive it, amounting to some 1.7 million people (Park-Lee et al., 2017). Chapter 3 examines the nature and extent of OUD and access to medications across subgroups of the population. The treatment gap widens further for vulnerable populations. For example, only 1 in 20 people with OUD

in prison receives treatment during incarceration, and opioid overdose is a leading cause of death in people who have recently been released (Binswanger et al., 2013; Krawczyk et al., 2017). Medication-based treatment is rare and unavailable for most pregnant women with OUD (Terplan et al., 2015). People with OUD in rural communities, which are hard hit by the opioid epidemic, often face administrative, infrastructural, and transportation barriers to accessing these medications (NRHA, 2017).

Around 2.5 million people received treatment at a specialty facility in 2016 for a substance use disorder (SUD) (Park-Lee et al., 2017).[2] The proportion of these facilities that offered any of the FDA-approved medications increased from only 20 percent in 2007 to 36 percent in 2016, mainly due to increases in offering buprenorphine and extended-release naltrexone. Only 6 percent of facilities offered all three medications in 2016 (Mojtabai et al., 2019). A 2015 study found that in 48 states and the District of Columbia, the rates of OUD exceeded buprenorphine treatment capacity (Jones et al., 2015). Chapter 4 describes evidence for implementing medication-based treatment for OUD in different care settings, including opioid treatment programs (OTPs), office-based, acute care, and criminal justice and other care settings.

The low usage rates of medications to treat OUD are a consequence of multiple barriers, which are discussed in Chapter 5. Medications to treat OUD remain highly stigmatized among the general public as well as among professionals who commonly interact with persons with OUD (Brondani et al., 2017; DeFlavio et al., 2015; Kennedy-Hendricks et al., 2016, 2017; Livingston et al., 2018; van Boekel et al., 2013). Most of these professionals receive inadequate education and training about OUD and its treatment (Merrill et al., 2002; Moran et al., 2017). Regulatory and policy barriers around methadone and buprenorphine—such as current buprenorphine waiver policies, patient limits, and restrictions on settings—also impede the expansion of medication for OUD. Finance and payment policies impose further restrictions on medications that can prevent patients from accessing medications (Clark and Baxter, 2013; Huskamp et al., 2018; Peters and Wengle, 2016).

CHARGE TO THE COMMITTEE AND STUDY SCOPE

In September 2018, the National Institute on Drug Abuse and the Substance Abuse and Mental Health Services Administration charged the

[2] These estimates are based on the Substance Abuse and Mental Health Services Administration's 2016 National Survey on Drug Use and Health (Ahrnsbrak et al., 2017). One limitation of the survey is that it does not currently measure the use of medications to treat OUD.

National Academies of Sciences, Engineering, and Medicine (the National Academies) with developing a Consensus Study Report to synthesize the current knowledge on medication-based treatment for OUD and to highlight gaps in the evidence base to guide future research, policy, and service provision; to ensure that evidence-based treatment is delivered effectively; and to help identify impediments to its wider adoption (see Box 1-3 for the full Statement of Task). The National Academies convened a 14-member ad hoc committee of experts in the fields of neurobiology, pharmacology, addiction medicine, psychology, social work, nursing, health policy, and epidemiology to respond to the charge based on their experience and knowledge in the treatment of OUD. The committee also included individuals with lived experience as patients and family members of individuals with OUD.

CONCEPTUAL FRAMEWORK AND KEY TERMS

Addiction is a chronic disease that involves compulsive or uncontrolled use of one or more substances in the face of negative consequences (HHS, 2016). As with other chronic medical conditions, a confluence of genetic,

BOX 1-3
Statement of Task

To support the dissemination of accurate patient-focused information about treatments for addiction and to help provide scientific solutions to the current opioid crisis, an ad hoc committee under the auspices of the National Academies of Sciences, Engineering, and Medicine will conduct a study of the evidence base on medication-assisted treatment (MAT)[a] for opioid use disorder (OUD). Specifically, the committee will

- Review current knowledge and gaps in understanding regarding the effectiveness of MAT for treating OUD;
- Examine available evidence on the range of parameters and circumstances in which MAT can be effectively delivered (e.g., duration of treatment, populations, settings, and Interventions to address social determinants of health as a component of MAT);
- Identify challenges in implementation and uptake; and
- Identify additional research needed on MAT for OUD.

Based on its review of the literature and input from the public workshop, the committee will develop a report with its findings and conclusions.

[a] See Box 1-1 for an explanation of the committee's decision to not use the term MAT in this report.

environmental, and social factors shape a person's vulnerability to addiction. These factors determine a person's propensity to start using drugs and to keep using them, as well as a person's susceptibility to the particular types of neurobiological changes in the brain that characterize the progression to addiction (Demers et al., 2014; Volkow and Muenke, 2012). Addiction to opioids or OUD results from changes in the brain caused by prolonged opioid use, which should be treated with individualized, multidisciplinary care similarly to how other chronic diseases, such as diabetes or asthma, are treated. Box 1-4 provides an overview of the diagnostic criteria for OUD in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*. OUD can be treated successfully, allowing a person to attain

BOX 1-4
Diagnostic Criteria for Opioid Use Disorder

The *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition,* defines opioid use disorder as the presence of two or more of the criteria shown below within a 12-month period. The severity is defined as mild if two to three criteria are met, moderate if four to five criteria are met, and severe if six or more criteria are met. (The final two criteria are not counted toward a diagnosis of prescription opioid use disorder.)

- Using larger amounts of opioids or over a longer period than was intended
- Persistent desire to cut down or unsuccessful efforts to control use
- Great deal of time spent obtaining, using, or recovering from use
- Craving, or a strong desire or urge to use opioids
- Failure to fulfill major role obligations at work, school, or home due to recurrent opioid use
- Continued use despite recurrent or persistent social or interpersonal problems caused or exacerbated by opioid use
- Giving up or reducing social, occupational, or recreational activities due to opioid use
- Recurrent opioid use in physically hazardous situations
- Continued opioid use despite physical or psychological problems caused or exacerbated by its use
- Tolerance (marked increase in amount; marked decrease in effect)*
- Withdrawal syndrome as manifested by cessation of opioids or use of opioids (or a closely related substance) to relieve or avoid withdrawal symptoms*

* These criteria do not apply to people taking opioids as prescribed by their medical provider.

SOURCE: Adapted from APA, 2013.

full functionality and a high quality of life (Volkow et al., 2014). However, a major gap exists between the scientific evidence around addictions and SUDs and the public perceptions of those issues. There is substantial stigma attached to being a person with OUD that is not generally applied to others with chronic diseases (Barry et al., 2014; Leshner, 1997), due in part to the negative social effects of drug use and addiction on the broader population (Humphreys, 2017). The stigmatization of OUD and medications to treat it is underpinned by the faulty premise that addiction is simply a moral failure, rather than a chronic condition that warrants appropriate evidence-based treatment (Kennedy-Hendricks et al., 2016, 2017).

There has been a growing understanding within the scientific research and medical communities that OUD and other SUDs are in fact chronic diseases susceptible to relapse and should be treated as such, rather than treating them only as episodic acute care incidents (Leshner, 1997; White et al., 2002). Tolerance and withdrawal symptoms are the hallmarks of prolonged opioid use. Over time, progressively higher doses of opioids are required to yield the same effect because the functional response of the brain's opioid receptors becomes impaired (Williams et al., 2013). Escalating tolerance due to chronic opioid use causes acute physical and psychological withdrawal symptoms that can develop within hours of discontinuation (Schuckit, 2016). Reduced tolerance after a period without opioids leads to an increased risk of overdose if the person returns to use with an opioid that has a relatively more potent effect (Strang et al., 2003). This explains, for example, the high overdose risk of former inmates after release from prison (Binswanger et al., 2007, 2013). People with OUD need treatment and support to cope with their symptoms during the acute withdrawal phase and to reduce their cravings and illicit opioid use during the maintenance phase. Research has shown that SUD treatment is more effective when viewed, like other chronic conditions, as requiring continuing care with treatment goals focused on management rather than a cure, defined as the total stopping of drug use for the rest of one's life (Humphreys and Tucker, 2002; McLellan et al., 2000; O'Brien and McLellan, 1996).

Underpinning the understanding of OUD as a chronic disease is the brain disease model of addiction. According to this model, SUDs are diseases of the brain because of the effects that those substances have on brain structure and function. Opioids target a naturally occurring opioid system in the brain that has evolved to play an important role in the control of pain, stress, reward, eating, sleep, emotions, and cognition (Brown et al., 2011; Elman and Borsook, 2016). The natural opioids, also known as endorphins or endogenous opioids, activate the brain's opioid receptors to produce their critical effects on brain function and behavior. Extensive neuroscience research has defined the key features of this natural system. These fea-

tures include the system's many component molecules,[3] their brain distribution, and the three classes of opioid receptors that mediate the actions of endogenous and exogenous opioids (Darcq and Kieffer, 2018; Valentino and Volkow, 2018). Prolonged opioid use may lead to OUD by superseding the actions of the natural endorphins at the opioid receptors, which can overtake the opioid system and prevent its ability to self-regulate. In a brain without OUD, the effects of endorphins are self-limited by numerous checks and balances, but repeated use of opioids can produce powerful and sustained effects that dramatically disrupt this regulation, resulting in tolerance, physical dependence, and addiction. Among their many effects, opioids initially produce positive feelings (or euphoria) not only through the stimulation of the mu-opioid receptor, but also through the subsequent release of the neurotransmitter dopamine in the brain's reward circuits. The dopamine system is one of several brain systems involved in drug reward processes (Koob, 1992). With repeated opioid use, the dopamine response becomes more "sensitized" (i.e., magnified after repeated exposures), which contributes to active craving of the drug (Robinson and Berridge, 2008). Over time, the use of opioids also dampens the influence of brain circuits tied to "executive function" and decision making that restrain drug-seeking behavior (Koob, 2006; Volkow et al., 2016). This combination of an increased drive for reward and craving coupled with the loss of inhibitory control can lead an individual to act impulsively and pursue instant gratification by consuming the drug.

The altered reward and cognitive processes in combination with the emergence of a chronic stress and negative mood state have been hypothesized to be responsible for a "dark side of addiction" (Koob, 2006), in which the attempts to alleviate negative emotions and the inability to feel pleasure that arise during non-intoxication periods contribute to compulsive drug-taking behavior. A particular component of the brain opioid system—the dynorphin-kappa system—has been strongly implicated in a persistent negative effect that is thought to drive continued drug use, craving, and relapse (Chavkin and Koob, 2016). Moreover, these changes to the brain continue even after an individual discontinues opioid use and no longer has symptoms of acute withdrawal, making long-term recovery more difficult (Leshner, 1997; Volkow et al., 2016).

Ultimately, the committee contends, framing OUD as a chronic disease that is responsive to treatment broadly available through the health care delivery system through a chronic disease management approach will help to decrease the stigma around OUD and allow more individuals to receive high-quality, long-term care. This conceptual framework requires precision and sensitivity to the terminology used to describe OUD; Box 1-5 presents a list of terms and definitions.

[3] Such as the endogenous opioid neuropeptides beta-endorphin, the enkephalins, and dynorphin.

BOX 1-5
Key Terms

Abstinence—This term typically is used to refer to not using alcohol or illicit drugs. This term is complex and often misused. This committee will not use this term, opting instead to using the term remission (see below).

Addiction—Another term for a substance use disorder, which is associated with compulsive or uncontrolled use of one or more substances in the face of negative consequences. Addiction is a chronic brain disease that has the potential for both recurrence and remission.

Agonist—A chemical substance that binds to and activates certain receptors on cells, causing a biological response. Methadone is an example of an opioid-receptor full agonist. Buprenorphine is an example of an opioid-receptor partial agonist.

Antagonist—A chemical substance that binds to and blocks the activation of certain receptors on cells, preventing a biological response. Naltrexone and naloxone are examples of opioid-receptor antagonists.

Behavioral interventions—Interventions (e.g., cognitive behavioral therapy, contingency management, structured family therapy) designed to engage people in opioid use disorder treatment, provide incentives to not use illicit opioids, modify attitudes and behaviors related to the use of opioids, and increase life skills to handle stressful circumstances and environmental cues that may trigger intense craving for opioids.

Dependence—A physical state in which an organism only functions normally in the presence of a substance and experiences physical disturbance when the substance is removed. A person can be dependent on a substance without being addicted, but dependence sometimes leads to addiction.

Diversion—A legal concept involving the transfer of any legally prescribed controlled substance from the person for whom it was prescribed to another person for illicit use.

Misuse—Use of any substance in a manner, situation, amount, or frequency that can cause harm to users. Medication misuse is the use of a medication in any way a doctor did not direct an individual to use it.

Opioid treatment program (OTP)—The Substance Abuse and Mental Health Services Administration–certified program, usually comprising a facility, staff, administration, patients, and services, that engages in the supervised assessment and treatment using methadone, buprenorphine, or naltrexone of individuals who have opioid use disorder. OTPs can exist in a number of settings, including but not limited to outpatient, residential, and hospital settings. Services may include

continued

BOX 1-5 Continued

medically supervised withdrawal or maintenance treatment as well as various levels of medical, psychiatric, psychosocial, and other types of supportive care.

Opioid use disorder (OUD)—The *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition,* defines OUD as a problematic pattern of opioid use leading to clinically significant impairment or distress, as manifested by at least 2 out of 11 criteria within a 12-month period. See Box 1-4 for the full list of diagnostic criteria for OUD.

Recovery—A process of change through which individuals improve their health and wellness, live self-directed lives, and strive to reach their full potential. Recovery is built on access to evidence-based clinical treatment and recovery support services.

Remission—A medical term meaning that major disease symptoms are eliminated or diminished below a pre-determined, harmful level.

Return to use—The return to drug use after a significant period without opioids, often referred to as relapse.

Tolerance—Alteration of the body's responsiveness to alcohol or a drug such that higher doses are required to produce the same effect achieved during initial use.

Treatment for opioid use disorder—A service or set of services that may include medication, behavioral interventions, and other supportive services designed to enable an individual to reduce or eliminate drug use, address associated physical or mental health problems, and restore one's maximum functional ability.

Withdrawal—A set of extreme physical symptoms that are experienced when discontinuing the use of a substance to which a person has become dependent or addicted, which can include nausea, vomiting, muscle aches, and cramping, among others, and stress, anxiety, and depression. Withdrawal symptoms often lead a person to use the substance again.

SOURCES: Adapted from HHS, 2016; NIDA, 2018; SAMSHA, 2012.

STUDY METHODOLOGY

The consensus study was carried out by the committee between October 2018 and March 2019. Study activities included a comprehensive literature review of the landscape of treatment for OUD; one 1.5-day public workshop held in Washington, DC, which was summarized in a Proceedings of a Workshop—in Brief; and two 2-day closed committee meetings. See Appendix A for a more detailed description of the study methodology.

ORGANIZATION OF THE CONSENSUS STUDY REPORT

The Consensus Study Report is structured into five chapters, including the introductory Chapter 1. Chapter 2, The Effectiveness of Medication-Based Treatment for Opioid Use Disorder, examines the evidence base, knowledge gaps, and future research needs for medications to treat OUD as well as for behavioral interventions in conjunction with medication for OUD. Chapter 3, Treatment with Medications for Opioid Use Disorder in Different Populations, surveys existing evidence and knowledge gaps related to the treatment of OUD across different subpopulations in the United States, including adolescents, older adults, pregnant women, persons with co-occurring conditions, racial and ethnic minorities, and people with low socioeconomic status. Chapter 4, Medications for Opioid Use Disorder in Various Treatment Settings, reviews the evidence concerning differences in medication access and use in different treatment settings including OTPs, office-based care, acute care settings, criminal justice, and other care settings. Finally, in Chapter 5, Barriers to Broader Use of Medications to Treat Opioid Use Disorder, the major barriers to full access and use are explored, including issues related to stigma, workforce education and training, law and regulation, and health care delivery and payment.

Conclusion 1:
Opioid use disorder is a treatable chronic brain disease.

OUD is a treatable chronic brain disease resulting from the changes in neural structure and function that are caused over time by repeated opioid use. The behavioral and social contexts are critically important to both its development and treatment. Stopping opioid misuse is extremely difficult. Medications are intended to normalize brain structure and function.

REFERENCES

Ahrnsbrak, R., J. Bose, S. L. Hedden, R. N. Lipari, and E. Park-Lee. 2017. *Key substance use and mental health indicators in the United States: Results from the 2016 National Survey on Drug Use and Health*. Substance Abuse and Mental Health Services Administration. https://www.samhsa.gov/data/sites/default/files/NSDUH-FFR1-2016/NSDUH-FFR1-2016.htm#sud7 (accessed February 9, 2019).

APA (American Psychiatric Association). 2013. *Diagnostic and statistical manual of mental disorders, fifth edition (DSM-5®)*. Washington, DC: American Psychiatric Publishing.

Axeen, S. 2018. Trends in opioid use and prescribing in Medicare, 2006–2012. *Health Services Research* 53(5):3309–3328.

Barry, C. L., E. E. McGinty, B. A. Pescosolido, and H. H. Goldman. 2014. Stigma, discrimination, treatment effectiveness, and policy: Public views about drug addiction and mental illness. *Psychiatric Services* 65(10):1269–1272.

Bart, G. 2012. Maintenance medication for opiate addiction: The foundation of recovery. *Journal of Addictive Diseases* 31(3):207–225.

Binswanger, I. A., M. F. Stern, R. A. Deyo, P. J. Heagerty, A. Cheadle, J. G. Elmore, and T. D. Koepsell. 2007. Release from prison—A high risk of death for former inmates. *New England Journal of Medicine* 356(2):157–165.

Binswanger, I. A., P. J. Blatchford, S. R. Mueller, and M. F. Stern. 2013. Mortality after prison release: Opioid overdose and other causes of death, risk factors, and time trends from 1999 to 2009. *Annals of Internal Medicine* 159(9):592–600.

Bohnert, A. S. B., M. Valenstein, M. J. Bair, D. Ganoczy, J. F. McCarthy, M. A. Ilgen, and F. C. Blow. 2011. Association between opioid prescribing patterns and opioid overdose-related deaths. *JAMA* 305(13):1315–1321.

Brondani, M. A., R. Alan, and L. Donnelly. 2017. Stigma of addiction and mental illness in healthcare: The case of patients' experiences in dental settings. *PLOS ONE* 12(5):e0177388.

Brown, E. N., P. L. Purdon, and C. J. Van Dort. 2011. General anesthesia and altered states of arousal: A systems neuroscience analysis. *Annual Review of Neuroscience* 34:601–628.

Carlson, R. G., R. W. Nahhas, S. S. Martins, and R. Daniulaityte. 2016. Predictors of transition to heroin use among initially non-opioid dependent illicit pharmaceutical opioid users: A natural history study. *Drug and Alcohol Dependence* 160:127–134.

CDC (U.S. Centers for Disease Control and Prevention). 2017. *New hepatitis C infections nearly tripled over five years*. https://www.cdc.gov/nchhstp/newsroom/2017/Hepatitis-Surveillance-Press-Release.html (accessed February 8, 2019).

CDC. 2018a. *Understanding the epidemic*. https://www.cdc.gov/drugoverdose/epidemic/index.html (accessed February 8, 2019).

CDC. 2018b. *U.S. drug overdose deaths continue to rise; increase fueled by synthetic opioids*. https://www.cdc.gov/media/releases/2018/p0329-drug-overdose-deaths.html (accessed February 8, 2019).

Chavkin, C., and G. F. Koob. 2016. Dynorphin, dysphoria, and dependence: The stress of addiction. *Neuropsychopharmacology* 41(1):373–374.

Cicero, T. J., M. S. Ellis, H. L. Surratt, and S. P. Kurtz. 2014a. The changing face of heroin use in the United States: A retrospective analysis of the past 50 years. *JAMA Psychiatry* 71(7):821–826.

Cicero, T. J., M. S. Ellis, H. L. Surratt, and S. P. Kurtz. 2014b. Factors contributing to the rise of buprenorphine misuse: 2008–2013. *Drug and Alcohol Dependence* 142:98–104.

Clark, R. E., and J. D. Baxter. 2013. Responses of state Medicaid programs to buprenorphine diversion: Doing more harm than good? *JAMA Internal Medicine* 173(17):1571–1572.

Council of Economic Advisers. 2017. *The underestimated cost of the opioid crisis*. Executive Office of the President of the United States. https://www.whitehouse.gov/sites/whitehouse.gov/files/images/The%20Underestimated%20Cost%20of%20the%20Opioid%20Crisis.pdf (accessed February 8, 2019).

Darcq, E., and B. L. Kieffer. 2018. Opioid receptors: Drivers to addiction? *Nature Reviews Neuroscience* 19(8):499–514.

DeFlavio, J. R., S. A. Rolin, B. R. Nordstrom, and L. A. Kazal, Jr. 2015. Analysis of barriers to adoption of buprenorphine maintenance therapy by family physicians. *Rural & Remote Health* 15:3019.

Demers, C. H., R. Bogdan, and A. Agrawal. 2014. The genetics, neurogenetics, and pharmacogenetics of addiction. *Current Behavioral Neuroscience Reports* 1(1):33–44.

Doran, K. M., N. Rahai, R. P. McCormack, J. Milian, D. Shelley, J. Rotrosen, and L. Gelberg. 2018. Substance use and homelessness among emergency department patients. *Drug and Alcohol Dependence* 188:328–333.

Elman, I., and D. Borsook. 2016. Common brain mechanisms of chronic pain and addiction. *Neuron* 89:11–36.

Florence, C. S., C. Zhou, F. Luo, and L. Xu. 2016. The economic burden of prescription opioid overdose, abuse, and dependence in the United States, 2013. *Medical Care* 54(10):901–906.

Gowing, L., M. F. Farrell, R. Bornemann, L. E. Sullivan, and R. Ali. 2011. Oral substitution treatment of injecting opioid users for prevention of HIV infection. *Cochrane Database of Systematic Reviews* 2011(8):CD004145.

Han, B., W. M. Compton, C. Blanco, E. Crane, J. Lee, and C. M. Jones. 2017. Prescription opioid use, misuse, and use disorders in U.S. adults: 2015 National Survey on Drug Use and Health. *Annals of Internal Medicine* 167(5):293–301.

Hedegaard, H., A. M. Miniño, and M. Warner. 2018. *Drug overdose deaths in the United States, 1999–2017*. National Center for Health Statistics, no. 329. Hyattsville, MD: National Center for Health Statistics. https://www.cdc.gov/nchs/products/databriefs/db329.htm (accessed February 8, 2019).

HHS (U.S. Department of Health and Human Services). 2016. *Facing addiction in America: The Surgeon General's report on alcohol, drugs, and health*. Washington, DC: U.S. Department of Health and Human Services.

Humphreys, K. 2017. How to deliver a more persuasive message regarding addiction as a medical disorder. *Journal of Addiction Medicine* 11(3):174–175.

Humphreys, K., and J. A. Tucker. 2002. Toward more responsive and effective intervention systems for alcohol-related problems. *Addiction* 97(2):126–132.

Huskamp, H. A., L. E. Riedel, C. L. Barry, and A. B. Busch. 2018. Coverage of medications that treat opioid use disorder and opioids for pain management in marketplace plans, 2017. *Medical Care* 56(6):505–509.

IOM (Institute of Medicine). 2011. *Relieving pain in America: A blueprint for transforming prevention, care, education, and research*. Washington, DC: The National Academies Press.

Jarvis, B. P., A. F. Holtyn, S. Subramaniam, D. A. Tompkins, E. A. Oga, G. E. Bigelow, and K. Silverman. 2018. Extended-release injectable naltrexone for opioid use disorder: A systematic review. *Addiction* 113(7):1188–1209.

Jones, C. M., M. Campopiano, G. Baldwin, and E. McCance-Katz. 2015. National and state treatment need and capacity for opioid agonist medication-assisted treatment. *American Journal of Public Health* 105(8):e55–e63.

Joszt, L. 2018. CDC data: Life expectancy decreases as deaths from suicide, drug overdose increase. In Focus blog. *American Journal of Managed Care*, November 30. https://www.ajmc.com/focus-of-the-week/cdc-data-life-expectancy-decreases-as-deaths-from-suicide-drug-overdose-increase (accessed February 8, 2019).

Kakko, J., K. D. Svanborg, M. J. Kreek, and M. Heilig. 2003. 1-year retention and social function after buprenorphine-assisted relapse prevention treatment for heroin dependence in Sweden: A randomised, placebo-controlled trial. *Lancet* 361(9358):662–668.

Kennedy-Hendricks, A., S. H. Busch, E. E. McGinty, M. A. Bachhuber, J. Niederdeppe, S. E. Gollust, D. W. Webster, D. A. Fiellin, and C. L. Barry. 2016. Primary care physicians' perspectives on the prescription opioid epidemic. *Drug and Alcohol Dependence* 165:61–70.

Kennedy-Hendricks, A., C. L. Barry, S. E. Gollust, M. E. Ensminger, M. S. Chisolm, and E. E. McGinty. 2017. Social stigma toward persons with prescription opioid use disorder: Associations with public support for punitive and public health-oriented policies. *Psychiatric Services* 68(5):462–469.

Ko, J. Y., S. W. Patrick, V. T. Tong, R. Patel, J. N. Lind, and W. D. Barfield. 2016. Incidence of neonatal abstience syndrome—28 states, 1999–2013. *Morbidity and Mortality Weekly Report* 65(31):799–802.

Kolodny, A., D. T. Courtwright, C. S. Hwang, P. Kreiner, J. L. Eadie, T. W. Clark, and G. C. Alexander. 2015. The prescription opioid and heroin crisis: A public health approach to an epidemic of addiction. *Annual Review of Public Health* 36(1):559–574.

Koob, G. F. 1992. Drugs of abuse: Anatomy, pharmacology and function of reward pathways. *Trends in Pharmacological Sciences* 13:177–184.

Koob, G. F. 2006. The neurobiology of addiction: A neuroadaptational view relevant for diagnosis. *Addiction* 101(Suppl 1):23–30.

Krawczyk, N., C. E. Picher, K. A. Feder, and B. Saloner. 2017. Only one in twenty justice-referred adults in specialty treatment for opioid use receive methadone or buprenorphine. *Health Affairs* 36(12):2046–2053.

Leshner, A. I. 1997. Addiction is a brain disease, and it matters. *Science* 278(5335):45–47.

Livingston, J. D., E. Adams, M. Jordan, Z. MacMillan, and R. Hering. 2018. Primary care physicians' views about prescribing methadone to treat opioid use disorder. *Substance Use & Misuse* 53(2):344–353.

Lyapustina, T., and G. C. Alexander. 2015. The prescription opioid addiction and abuse epidemic: How it happened and what we can do about it. *The Pharmaceutical Journal* 294(7866), online. doi: 10.1211/PJ.2015.20068579.

Mattick, R. P., C. Breen, J. Kimber, and M. Davoli. 2009. Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. *Cochrane Database of Systematic Reviews* 2009(3):CD002209.

Mattick, R. P., J. Kimber, C. Breen, and M. Davoli. 2014. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *Cochrane Database of Systematic Reviews* 2014(2):CD002207.

McLellan, A. T., D. C. Lewis, C. P. O'Brien, and H. D. Kleber. 2000. Drug dependence, a chronic medical illness: Implications for treatment, insurance, and outcomes evaluation. *JAMA* 284(13):1689–1695.

Merrill, J. O., L. A. Rhodes, R. A. Deyo, G. A. Marlett, and K. A. Bradley. 2002. Mutual mistrust in the medical care of drug users: The keys to the "narc" cabinet. *Journal of General Internal Medicine* 17(5):327–333.

Mojtabai, R., C. Mauro, M. M. Wall, C. L. Barry, and M. Olfson. 2019. Medication treatment for opioid use disorders in substance use treatment facilities. *Health Affairs* 38(1). doi: 10.1377/hlthaff.2018.05162.

Moran, G. E., C. M. Snyder, R. F. Noftsinger, and J. K. Noda. 2017. *Implementing medication-assisted treatment for opioid use disorder in rural primary care: Environmental scan, volume 1*. AHRQ Publication No. 17(18)-0050-EF. Rockville, MD: Agency for Healthcare Research and Quality. https://integrationacademy.ahrq.gov/sites/default/files/mat_for_oud_environmental_scan_volume_1_1.pdf (accessed February 8, 2019).

Muhuri, P. K., J. C. Gfroerer, and M. C. Davies. 2013. Associations of nonmedical pain reliever use and initiation of heroin use in the United States. *CBHSQ Data Review*, August. https://www.samhsa.gov/data/sites/default/files/DR006/DR006/nonmedical-pain-reliever-use-2013.htm (accessed February 7, 2019).

NASEM (National Academies of Sciences, Engineering, and Medicine). 2017. *Pain management and the opioid epidemic: Balancing societal and individual benefits and risks of prescription opioid use*. Washington, DC: The National Academies Press.

NIDA (National Institute on Drug Abuse). 2018. *Principles of drug addiction treatment: A research-based guide (third edition)*. Rockville, MD: National Institutes of Health.

NRHA (National Rural Health Association). 2017. *Treating the rural opioid epidemic*. National Rural Health Association Policy Brief. https://www.ruralhealthweb.org/NRHA/media/Emerge_NRHA/Advocacy/Policy%20documents/Treating-the-Rural-Opioid-Epidemic_Feb-2017_NRHA-Policy-Paper.pdf (accessed February 8, 2019).

O'Brien, C., and A. T. McLellan. 1996. Myths about the treatment of addiction. *Lancet* 347(8996):237–240.

Park-Lee, E., R. N. Lipari, S. L. Hedden, L. A. Kroutil, and J. D. Porter. 2017. *Receipt of services for substance use and mental health issues among adults: Results from the 2016 National Survey on Drug Use and Health*. Substance Abuse and Mental Health Services Administration. https://www.samhsa.gov/data/sites/default/files/NSDUH-DR-FFR2-2016/NSDUH-DR-FFR2-2016.htm (accessed February 8, 2019).

Patrick, S. W., M. M. Davis, C. U. Lehmann, and W. O. Cooper. 2015. Increasing incidence and geographic distribution of neonatal abstinence syndrome: United States, 2009 to 2012. *Journal of Perinatology* 35(8):650–655.

Peters, R., and E. Wengle. 2016. Coverage of substance-use disorder treatments in marketplace plans in six cities. In *ACA Implementation—Monitoring and Tracking*: The Urban Institute. https://www.rwjf.org/en/library/research/2016/06/coverage-of-substance-use-disorder-treatments-in-marketplace-pla.html (accessed February 8, 2019).

Radel, L., M. Baldwin, G. Crouse, R. Ghertner, and A. Waters. 2018. *Substance use, the opioid epidemic, and the child welfare system: Key findings from a mixed methods study.* U.S. Department of Health and Human Services. https://aspe.hhs.gov/system/files/pdf/258836/SubstanceUseChildWelfareOverview.pdf (accessed February 8, 2019).

Robinson, T. E., and K. C. Berridge. 2008. The incentive sensitization theory of addiction: Some current issues. *Philosophical Transactions of the Royal Society of London, B: Biological Sciences* 363(1507):3137–3146.

SAMHSA (Substance Abuse and Mental Health Services Administration). 2012. *SAMHSA's working definition of recovery: 10 guiding principles of recovery*. https://store.samhsa.gov/system/files/pep12-recdef.pdf (accessed February 8, 2019).

Schuckit, M. A. 2016. Treatment of opioid-use disorders. *New England Journal of Medicine* 375(4):357–368.

Schwartz, R. P., J. Gryczynski, K. E. O'Grady, J. M. Sharfstein, G. Warren, Y. Olsen, S. G. Mitchell, and J. H. Jaffe. 2013. Opioid agonist treatments and heroin overdose deaths in Baltimore, Maryland, 1995–2009. *American Journal of Public Health* 103(5):917–922.

Seth, P., L. Scholl, R. A. Rudd, and S. Bacon. 2018. Overdose deaths involving opioids, cocaine, and psychostimulants–United States, 2015–2016. *Morbidity and Mortality Weekly Report* 67(12):349–358.

Strang, J., J. McCambridge, D. Best, T. Beswick, J. Bearn, S. Rees, and M. Gossop. 2003. Loss of tolerance and overdose mortality after inpatient opiate detoxification: Follow-up study. *BMJ* 326(7396):959–960.

Terplan, M., N. Longinaker, and L. Appel. 2015. Women-centered drug treatment services and need in the United States, 2002–2009. *American Journal of Public Health* 105(11):e50–e54.

Thomas, C. P., C. A. Fullerton, M. Kim, L. Montejano, D. R. Lyman, R. H. Dougherty, A. S. Daniels, S. S. Ghose, and M. E. Delphin-Rittmon. 2014. Medication-assisted treatment with buprenorphine: Assessing the evidence. *Psychiatric Services* 65(2):158–170.

Timko, C., N. R. Schultz, M. A. Cucciare, L. Vittorio, and C. Garrison-Diehn. 2016. Retention in medication-assisted treatment for opiate dependence: A systematic review. *Journal of Addictive Diseases* 35(1):22–35.

Valentino, R. J., and N. D. Volkow. 2018. Untangling the complexity of opioid receptor function. *Neuropsychopharmacology* 43(13):2514–2520.

van Boekel, L. C., E. P. Brouwers, J. van Weeghel, and H. F. Garretsen. 2013. Stigma among health professionals towards patients with substance use disorders and its consequences for healthcare delivery: Systematic review. *Drug and Alcohol Dependence* 131(1–2):23–35.

Volkow, N. D., and M. Muenke. 2012. The genetics of addiction. *Human Genetics* 131(6):773–777.

Volkow, N. D., T. R. Frieden, P. S. Hyde, and S. S. Cha. 2014. Medication-assisted therapies—Tackling the opioid-overdose epidemic. *New England Journal of Medicine* 370(22):2063–2066.

Volkow, N. D., G. F. Koob, and A. T. McLellan. 2016. Neurobiologic advances from the brain disease model of addiction. *New England Journal of Medicine* 374(4):363–371.

Volkow, N. D., E. B. Jones, E. B. Einstein, and E. M. Wargo. 2018. Prevention and treatment of opioid misuse and addiction: A review. *JAMA Psychiatry*, December 5 [Epub ahead of print].

Vowles, K. E., M. L. McEntee, P. S. Julnes, T. Frohe, J. P. Ney, and D. N. van der Goes. 2015. Rates of opioid misuse, abuse, and addiction in chronic pain: A systematic review and data synthesis. *Pain* 156(4):569–576.

Weiss, A. J., and K. C. Heslin. 2018. *Payers of opioid-related inpatient stays and emergency department visits nationally and by state, 2010 and 2015*. Healthcare Cost and Utilization Project. https://hcup-us.ahrq.gov/reports/statbriefs/sb239-Opioid-Payer-Hospital-Stays-ED-Visits-by-State.jsp (accessed February 8, 2019).

White, W. L., M. Boyle, and D. Loveland. 2002. Alcoholism/addiction as a chronic disease. *Alcoholism Treatment Quarterly* 20(3–4):107–129.

Williams, J. T., S. L. Ingram, G. Henderson, C. Chavkin, M. von Zastrow, S. Schulz, T. Koch, C. J. Evans, and M. J. Christie. 2013. Regulation of mu-opioid receptors: Desensitization, phosphorylation, internalization, and tolerance. *Pharmacological Reviews* 65(1):223–254.

Woody, G. E., D. Bruce, P. T. Korthuis, S. Chhatre, S. Poole, M. Hillhouse, P. Jacobs, J. Sorensen, A. J. Saxon, D. Metzger, and W. Ling. 2014. HIV risk reduction with buprenorphine-naloxone or methadone: Findings from a randomized trial. *Journal of Acquired Immune Deficiciency Syndromes* 66(3):288–293.

Yang, B. K., C. L. Storr, A. M. Trinkoff, M. Sohn, S. K. Idzik, and M. McKinnon. 2018. National opioid prescribing trends in emergency departments by provider type: 2005–2015. *American Journal of Emergency Medicine*, October 22 [Epub ahead of print].

2

The Effectiveness of Medication-Based Treatment for Opioid Use Disorder

U.S. Food and Drug Administration–approved medications to treat opioid use disorder are effective and save lives. Long-term retention on medication for OUD is associated with improved outcomes. A lack of availability of behavioral interventions is not a sufficient justification to withhold medications to treat OUD.

Methadone, buprenorphine, and extended-release naltrexone are the three medications currently approved by the U.S. Food and Drug Administration (FDA) for treating opioid use disorder (OUD). Box 2-1 provides a full list of them. All three medications reduce opioid cravings and help to sever the ties between opioid use and established situational or emotional triggers. These medications work by targeting the mu-opioid receptor within the endogenous opioid system, although each has a distinct mechanism of action. Their safety and efficacy profiles differ due to their differing pharmacological, pharmacodynamic, and pharmacokinetic properties (Connery, 2015; Kleber, 2007). This chapter examines the evidence base for the effectiveness of these three medications as well as identifying gaps in knowledge and future research needs. The chapter also explores the use of behavioral interventions in conjunction with medications to treat OUD.

METHADONE

Methadone is a synthetic, long-lasting opioid agonist (Kreek, 2000). Methadone fully activates the mu-opioid receptors in the brain through the same mechanism of action as prescription or illicit opioids. In persons with

BOX 2-1
U.S. Food and Drug Administration–Approved Medications for the Treatment of Opioid Use Disorder

FDA-approved methadone products include

- Methadone hydrochloride, tablets (Dolophine; generic available)
- Methadone hydrochloride, oral concentrate (Methadose; generic available)

FDA-approved buprenorphine products include

- Buprenorphine and naloxone, buccal film (Bunavail)
- Buprenorphine and naloxone, sublingual film (Cassipa, Suboxone, generics available)
- Buprenorphine and naloxone, sublingual tablets (Zubsolv, generics available)
- Buprenorphine implant for subdermal administration (Probuphine)
- Buprenorphine extended-release, injection for subcutaneous use (Sublocade)
- Buprenorphine, sublingual tablet (formerly under trade name subutex, generics available)

FDA-approved naltrexone products include

- Naltrexone for extended-release injectable suspension, intramuscular (Vivitrol)

SOURCE: Adapted from FDA, 2018.

OUD, methadone occupies those mu-opioid receptors and has the effect of lessening the painful "lows" of opioid withdrawal, and, at therapeutic doses, it attenuates the euphoric "highs" of shorter-acting opioids such as heroin, codeine, and oxycodone. Because it is an agonist treatment and individuals do not have to go through opioid withdrawal before initiating it, methadone can be started at any time during OUD treatment. However, it does require days to weeks to achieve a therapeutic dose, which needs to be individualized to decrease cravings and prevent return to other opioid use (NIH, 1998).

By law in the United States, outpatient methadone treatment can only be administered to people enrolled in state- and federally certified opioid treatment programs (OTPs), historically called methadone clinics; methadone can also be provided when patients are admitted to a hospital for treatment of other conditions or in emergencies (CRS, 2018). Most patients are required to visit an OTP in person every day to receive their daily dose. Eventually, stable patients may receive take-home doses if they meet certain criteria, such as having had a stable period of good functioning without illicit drug use. In addition, patients on methadone are required to attend regular counseling sessions with clinic providers.

As an agonist, methadone sustains the opioid tolerance and physical dependence of the patient, so missing doses can cause opioid withdrawal. The major risk to patients on methadone—opioid overdose death—is elevated within the first 2 weeks of methadone treatment (Degenhardt et al., 2009), after which the risk of overdose death is significantly lower than for people with OUD who are not in treatment (Degenhardt et al., 2011; Sordo et al., 2017). The risk of overdose is higher among patients who are also taking other sedatives, but FDA has advised that "methadone should not be withheld from patients taking benzodiazepines or other drugs that depress the central nervous system" because overdose risk is even higher for people who are not on medication for OUD (FDA, 2017). This is also true of buprenorphine (see below). The other potential harms of methadone include hypogonadism (low testosterone), which is a common side effect of chronic use of any opioid (Bawor et al., 2015), and an increase in the electrocardiographic corrected QT interval, although the clinical significance of the latter is unclear (Bart et al., 2017). No special training is required for physicians working within an OTP to prescribe methadone.

BUPRENORPHINE

Buprenorphine is a high-affinity partial opioid agonist as well as an antagonist of the kappa-opioid receptor and an agonist of the opioid like-1 receptor (Kleber, 2007). As a partial agonist, buprenorphine does not fully substitute for other opioids on the mu receptor (e.g., heroin, codeine, and

oxycodone). Like methadone, buprenorphine can bring relief to a patient in opioid withdrawal. Through its partial agonist effect, it can also reduce the rewarding effect if the patient uses opioids while taking buprenorphine. Because it is a partial agonist, buprenorphine also has less of an effect on respiratory depression, so it has a lower risk of overdose than methadone and other opioids (Dahan et al., 2006), and a therapeutic dose may be achieved within a few days (Connery, 2015).

The most widely available forms of buprenorphine in the United States are tablets or films that are absorbed under the tongue (see Box 2-1). In these formulations, buprenorphine is combined with the opioid antagonist naloxone to discourage injection, because naloxone is not well absorbed sublingually but will rapidly reduce the rewarding effect if the product is injected. Buprenorphine is also available in implantable and extended-release subcutaneous formulations, which are more difficult to divert[1] and theoretically increase adherence to treatment.

In the United States, buprenorphine can also be provided at an OTP, but it is most commonly prescribed in an office-based setting (e.g., a primary care clinic) to patients who fill the prescription at regular pharmacies. Patients can then administer buprenorphine sublingually to themselves, as with most other medications for chronic disease. Patients are often seen by providers frequently at first, but as the treatment progresses patients who do not use other opioids are usually able to reduce the frequency of the required office visits (Fiellin et al., 2006). In order to treat OUD with buprenorphine, prescribers in the United States must undergo additional training and obtain a waiver from the Drug Enforcement Administration. Only a limited number of providers pursue these waivers. In fact, only 2 to 3 percent of physicians in the United States are waivered to provide buprenorphine, most of whom are based in urban areas (Jones et al., 2015). In 2017 nurse practitioners and physician assistants became eligible to apply for training to obtain waivers (ASAM, 2016). Chapter 5 includes a more detailed discussion on this issue.

As with methadone, buprenorphine sustains opioid tolerance and physical dependence in patients, so discontinuation can lead to withdrawal—although buprenorphine's withdrawal syndrome may be less severe. The most prominent risk of buprenorphine to patients with OUD is precipitation of non-life-threatening opioid withdrawal at first dose. The risk of opioid overdose death declines immediately when patients with OUD initiate buprenorphine treatment (Sordo et al., 2017). Hypogonadotropic effects are less with buprenorphine than with methadone and buprenorphine is not

[1] Diversion is a legal concept involving the transfer of any legally prescribed controlled substance from the person for whom it was prescribed to another person for illicit use (see Box 1-5).

associated with QTc prolongation or cardiac arrhythmias (Fareed et al., 2013).

It is important to note that since methadone and buprenorphine are opioids, they can be misused. As with other opioids, buprenorphine and methadone can result in physical dependence and a diagnosable OUD, which demands that these medications be safely stored and not be taken by anyone other than the individual for whom they are prescribed.

EXTENDED-RELEASE NALTREXONE

Naltrexone is not an opioid but rather is a full antagonist of the mu-opioid receptor and completely blocks the euphoric and analgesic effects of all opioids (Kleber, 2007). Naltrexone does not cause physical dependence, nor does it produce any of the rewarding effects of opioids. It is not uncommon for patients to try to use opioids while on extended-release naltrexone, but it is exceedingly rare that using an opioid can override the effect of naltrexone to the extent that the opioid yields rewarding effects. Ideally, patients on extended-release naltrexone learn quickly not to use the opioids that caused their addictive behaviors, and, after sustained use of the medication, their cravings decline (Krupitsky et al., 2011; Lee et al., 2018; Tanum et al., 2017).

Treatment initiation with extended-release naltrexone is complicated by its mechanism and long duration of action. Because naltrexone can trigger severe withdrawal symptoms, naltrexone treatment initiation typically requires medically supervised withdrawal followed by at least 4 to 7 days without any opioids, including opioids used in medication-based treatment like methadone and buprenorphine (Sullivan et al., 2017). This remains a key barrier to naltrexone use, although shorter outpatient initiation protocols have shown some promise (Sullivan et al., 2017). Risk of overdose for patients being treated with extended-release naltrexone may be reduced compared to treatment with a placebo, non-medication-based treatments, and treatment with oral naltrexone (Kelty and Hulse, 2017; Lee et al., 2016). Emerging evidence suggests that patients can experience an increased risk of overdose when they approach the end of the 28-day period of the extended-release formulation (Binswanger and Glanz, 2018).

Naltrexone is currently available both in a once-daily oral formulation and in a once-monthly, extended-release depot injection. The oral formulation was found to be no better than a placebo in retaining patients in treatment or eliminating their opioid use (Minozzi et al., 2011) and patients treated with oral naltrexone have an increased risk of overdose (Degenhardt et al., 2015). Thus, only the extended-release formulation has been approved for OUD by FDA. No special training is required for medical providers to prescribe naltrexone.

Naltrexone may be most appropriate for patients who need to avoid opioid agonists of any kind (including methadone and buprenorphine); patients who have not returned to use in 2 or more weeks but are at heightened risk of relapse; and patients who use opioids sporadically or at low levels. Naltrexone, unlike other OUD therapies, is not appropriate for the treatment of severe, acute pain—like that caused by a fractured bone or necessary surgery—because the medication completely blocks the effects of opioids. Depression is a relatively rare adverse effect of naltrexone and not a contraindication to its use (Dean et al., 2006).

NALOXONE

The opioid antagonist naloxone is not a medication for OUD per se, but it has been approved by FDA to diagnose or treat the respiratory depressive symptoms of opioid use that can cause fatal opioid overdose. Naloxone is safe and effective, and it is the standard medication administered to reverse opioid overdose. The broader provision of naloxone has been shown to prevent opioid overdose morbidity and mortality (Bird et al., 2016; Coffin et al., 2016). In every state and the District of Columbia, naloxone can be obtained from a pharmacy without having to see a prescriber (Davis and Carr, 2017; Green et al., 2015), and it is available from many community-based organizations and health departments for low or no cost (Wheeler et al., 2015). Notably, guidance from the U.S. Department of Health and Human Services[2] urges that all patients receiving medications for OUD be co-prescribed naloxone (HHS, 2018).

EVIDENCE ON THE EFFECTIVENESS OF FDA-APPROVED MEDICATIONS IN TREATING OUD

A wealth of evidence about medications to treat OUD has been amassed over the past half century from clinical studies, randomized controlled trials, systematic reviews, and meta-analyses. The verdict is clear: effective agonist medication used for an indefinite period of time is the safest option for treating OUD. According to a recent review of medications to treat OUD, "the evidence for efficacy both in reducing opioid use and retaining patients in care is strongest for agonist treatment" (Connery, 2015, p. 64).

People with OUD are less likely to die when they are in long-term treatment with methadone or buprenorphine than when they are untreated.

[2] This guidance also recommends that prescribers co-prescribe naloxone to patients at risk of overdose, patients taking benzodiazepines and opioids at any dosage, patients with a history of substance use disorder or prior overdose, and members of certain populations whose changes in opioid tolerance render them at great overdose risk, such as people leaving incarceration.

Treatment using agonist medication is estimated to reduce mortality by up to 50 percent among people with OUD (Cicero et al., 2014; Schuckit, 2016). Both methadone and buprenorphine treatment retention have been linked to substantially decreased risks of both all-cause and overdose-related mortality among people with OUD (Schuckit, 2016), and both medications reduce the number of opioid overdose deaths in the community (Pierce et al., 2016; Schwartz et al., 2013). Expanding access to these medications reduces the number of deaths due to opioid overdose (Cicero et al., 2014; Larochelle et al., 2017; Sordo et al., 2017). Studies of extended-release naltrexone have not had sufficient power or duration of follow-up to detect a mortality benefit (Jarvis et al., 2018).

Treatment with methadone or buprenorphine is also associated with lower rates of other opioid use (Kakko et al., 2003; Mattick et al., 2009, 2014; Thomas et al., 2014), improved social functioning (Bart, 2012), decreased injection drug use (Woody et al., 2014), reduced HIV transmission risk behaviors (Gowing et al., 2011), reduced risk of HIV diagnosis (MacArthur et al., 2012), reduced risk of hepatitis C virus (HCV) infection (Peles et al., 2011), and better quality of life compared to individuals with OUD not in treatment (Ponizovsky and Grinshpoon, 2007). Methadone is also associated with reduced levels of criminality for individuals with OUD (Bukten et al., 2012; Gearing, 1974; Schwartz et al., 2009, 2011; Sun et al., 2015). Limited evidence suggests that, compared with a placebo, extended-release naltrexone may be associated with reduced opioid use, but more rigorous studies are needed (Jarvis et al., 2018).

Compared with a placebo, both buprenorphine alone and buprenorphine in combination with naloxone administered in office-based treatment settings significantly reduce opioid use and opioid cravings (Fudala et al., 2003). In women who are pregnant, buprenorphine treatment has been linked to improved maternal and fetal outcomes; infants also tend to have less severe symptoms of neonatal abstinence syndrome when their mothers were treated with buprenorphine during pregnancy (Thomas et al., 2014).

Optimal Medication Dosing Range and Duration of Treatment

Treatment retention with agonist medications is dose related, with meta-analyses indicating that methadone doses must exceed 60 mg and that smaller doses may be no better than placebo (Bao et al., 2009). Buprenorphine dosing at 12–16 mg increases treatment retention, and higher doses result in better outcomes (Hser et al., 2014), better treatment retention (Bart et al., 2012), and reductions in heroin and cocaine use (Faggiano et al., 2003). Retention in treatment with naltrexone is dependent on formulation rather than dose. A meta-analysis of trials found that oral, short-acting naltrexone was not superior to a placebo in retaining people in treatment (Minozzi et al., 2011).

On the other hand, the optimal duration of medication for OUD has not been established. All studies of tapering and discontinuation demonstrate very high rates of relapse, although some patients may be able to successfully taper off without a return to use. Few definitive studies have been conducted because long-term treatment—particularly with methadone or buprenorphine—is complicated by stigma and misconceptions among patients and providers alike (see also Chapter 5). Nevertheless, multiple studies with longer-term follow-up indicate that extending treatment for years allows individuals to increase their opportunities to return to work, to regain their health, to avoid involvement with the criminal justice system, and to establish supportive networks of non-drug-using individuals (Eastwood et al., 2017; Goldstein and Herrera, 1995; Gossop et al., 2003; Hser et al., 2001; Simpson et al., 1982).

Retention in Treatment

While a large proportion of people with OUD return to use at some point in their lives, the risk of death is mitigated by remaining in treatment. Given the consequences of returning to use without the protective effect of either a high opioid tolerance or treatment with an antagonist, most people would likely benefit from long-term maintenance treatment (Kleber, 2007). The period immediately after treatment discontinuation is a particularly high overdose risk period, as is the first 4 weeks of methadone treatment (with risks for the latter decreasing substantially after week 4), underlining the significance of efforts to enhance retention (Manhapra et al., 2017; Sordo et al., 2017). A recent systematic review found substantial variability in retention rates across treatment settings but reported that, overall, only 37 percent of individuals initiating treatment with medication for OUD were retained in treatment after the 12-month follow-up (Timko et al., 2016). Discontinuation rates are high across all medications, and most discontinuation occurs early after starting treatment.

Systematic reviews of comparative studies suggest that methadone is associated with better retention in treatment and greater patient satisfaction than other medications for OUD (Ali et al., 2017). A review of 11 randomized controlled trials found that, compared with a placebo or nonpharmacological therapy, people who received methadone were more than four times more likely to stay in treatment and had significantly lower rates of heroin use (Mattick et al., 2009). The evidence base for buprenorphine—in particular, the extended-release formulations—is not as extensive as for methadone, but it suggests that treatment with buprenorphine may have an overall mortality benefit that is slightly less than treatment with methadone (Sordo et al., 2017), possibly driven by the lower rate of retention in buprenorphine treatment. While buprenorphine maintenance treat-

ment is at least as effective as methadone in suppressing the use of illicit opioids among people who remain in treatment, it appears to be slightly less effective than methadone maintenance treatment at retaining people in treatment (Mattick et al., 2014).

In contrast to methadone and buprenorphine, there have been fewer randomized controlled trials and thus less evidence about the effectiveness of extended-release naltrexone at retaining patients in treatment. Clinical studies demonstrate that oral naltrexone tends to have poorer long-term treatment adherence (Dunn et al., 2015) as well as higher mortality rates after treatment discontinuation than methadone (Degenhardt et al., 2015). A recent systematic review of 34 studies of extended-release naltrexone (Jarvis et al., 2018) reported that in controlled trials only 63 percent of individuals randomized to extended-release naltrexone successfully received even a single dose of medication—the equivalent of 4 weeks of treatment. In real-world community treatment settings, only 10.5 percent of patients were adherent to extended-release naltrexone at 6 months (Jarvis et al., 2018). The only controlled trial from the United States comparing extended-release naltrexone to buprenorphine found that "in the intention-to-treat population of all patients who were randomly assigned, XR-NTX [extended-release naltrexone] had lower relapse-free survival than BUP-NX [buprenorphine-naloxone]" (Lee et al., 2018, p. 315). In the intention-to-treat analysis, the proportion of opioid-relapse events was 65 percent for extended-release naltrexone compared with 57 percent for buprenorphine treatment; the authors attribute this difference to a lower rate of patients successfully beginning the treatment in the extended-release naltrexone group, because relapse-free survival rates were similar across the groups for patients who received at least one dose (Lee et al., 2018). Among patients who have already been withdrawn completely from opioids, retention among patients randomized to buprenorphine or extended-release naltrexone is similar (Lee et al., 2018; Tanum et al., 2017), but in the real world, patients offered all three medications seldom select extended-release naltrexone (Green et al., 2018; Vermont Department of Health, 2018). A recent report on the use of naltrexone and buprenorphine in a large U.S. commercially insured population reported that 52 percent of individuals treated with extended-release naltrexone and 31 percent of individuals treated with sublingual buprenorphine discontinued treatment after only 1 month (Morgan et al., 2018). Strategies to improve retention are needed across all forms of medication-based treatment.

KNOWLEDGE GAPS AND FUTURE DIRECTIONS FOR RESEARCH ON MEDICATIONS FOR OUD

In spite of the extensive evidence supporting the use of medications to treat OUD, there remain major gaps in knowledge about which medication

works best and for whom as well as how the medications compare over the long term. Additionally, as with all medical disorders, there is a need to expand the OUD treatment toolkit to help individuals who do not respond well to the current options.

Understanding Functional Outcomes of Medication-Based Treatment for OUD

A recent RAND systematic review of functional outcomes for individuals with OUD who were treated with medications found only 30 randomized trials and 10 high-quality observational studies that reported on at least one functional outcome in the five areas targeted: cognitive, physical, social/behavioral (including criminal), occupational, and neurological outcomes (Maglione et al., 2018). Maglione and colleagues noted that the lack of high-quality trials precluded a full meta-analytic approach to the available data or the ability to infer strong conclusions regarding the effects of medications for OUD on these important areas. Most of the evidence emerged from studies of methadone or buprenorphine treatment; few studies of functional outcomes after naltrexone were available. Moreover, the majority of the studies were cross-sectional with no follow-up data, and other reviews reporting patient-reported functional outcomes (e.g., health-related quality of life measures) are uncommon (Maglione et al., 2018).

Additional research and head-to-head trials are needed on the FDA-approved medications for OUD, particularly studies comparing the new formulations of the medications over the long term. Research is needed to assess more fully the medications' relative effects on brain functions (e.g., executive function, working memory, mood regulation, sleep architecture) and social outcomes, including those related to work, education, and family relationships. There is also a need for research focusing on optimal strategies for induction (for extended-release naltrexone) and retention (for all three medications) to improve the percentage of people retained in treatment (Kimber et al., 2015). For example, clonidine and lofexidine are alpha-2-adrenergic agonists administered to relieve opioid withdrawal symptoms after abrupt discontinuation of opioid use. Clonidine is suggested for use in conjunction with naltrexone or buprenorphine to reduce opioid withdrawal symptoms (Kleber, 2007; O'Connor and Kosten, 1998). Although it is not approved in the United States for treating opioid withdrawal, clonidine is used extensively off-label and the American Society of Addiction Medicine has recommended its inclusion in practice guidelines for managing withdrawal symptoms (Kampman and Jarvis, 2015). In 2018, lofexidine became the first non-opioid medication approved by FDA for reducing opioid withdrawal symptoms (Doughty et al., 2019; Fishman et al., 2018). Lofexidine could be used to support patients during naltrexone

induction or to treat withdrawal symptoms in patients who are not yet ready to begin an opioid agonist medication-based treatment for OUD. Extended-release medications for OUD have the potential to help overcome some of the problems of poor treatment adherence to daily medications. Potential research directions could include further investigations of how the real-world effectiveness of subcutaneous or implantable buprenorphine compares with extended-release naltrexone and which have the potential to substantially extend the dosing window and eliminate the burden of daily oral dosing. More fundamentally, comparing the effectiveness of sublingual and extended-release buprenorphine formulations would test the assumption that daily dosing is inferior.

Real-World Evidence on Patient Preferences

Patients' preferences about medications to treat OUD are fundamental in determining whether they start and stay on treatment for OUD, but those preferences have yet to be fully explored. Some informative data about patients' medication preferences are available from Rhode Island's correctional system and the state of Vermont. In both populations, methadone is the most common choice among people receiving medication for OUD (between 60 and 70 percent), with buprenorphine preferred by the remainder of patients. Only two people in Vermont and four people in Rhode Island's prison system have chosen treatment with extended-release naltrexone, according to recent data (Green et al., 2018; Vermont Department of Health, 2018). With extremely limited access to medications for OUD, however, patients may not be offered medication at all, much less be offered a choice between the FDA-approved medication options. Real-world evidence could help to elucidate the role of patient choice in the success of long-term treatment. Patients entering treatment often have strong preferences for one medication or another (Uebelacker et al., 2016), although many individuals entering treatment have limited knowledge regarding the available medications to treat OUD (Alves and Winstock, 2011). Increasing medication access, uptake, and retention will require taking patients' beliefs and preferences about medications into account (Uebelacker et al., 2016). Through shared decision making, a patient's preferences, goals, and motivations can be used to guide the choice of medication for OUD treatment.

Expanding the Number of OUD Treatment Medications

Expanding the treatment toolkit for OUD has the potential to increase treatment rates and provide more effective, individualized care for people with OUD. Treatment options that warrant further exploration include slow-release oral morphine (SROM), supervised injectable opioid agonist

therapies (siOAT), cannabinoids, and anti-opioid vaccines, to name a few. Many of these options would require not just approval by FDA, but also changes to the Harrison Narcotics Tax Act of 1914.[3]

Slow-Release Oral Morphine

SROM is a full agonist opioid with a slow-release oral formulation that has been proposed as an alternative maintenance therapy for people who do not respond adequately to the other available types of medications to treat OUD. As yet, no definitive evidence indicates that SROM is equivalent or superior as a treatment option, but SROM appeared to be similar in effectiveness to methadone in one study that directly compared the two for maintenance treatment (Beck et al., 2014). A systematic review found that although the evidence is very limited, SROM had similar retention rates to methadone in one study, and in other studies it was associated with improving quality of life, relieving withdrawal symptoms and cravings, and reducing other drug use (Jegu et al., 2011). Another systematic review suggested that SROM may reduce opioid use and depressive symptoms, but adverse effects were more frequent than for other types of medications for OUD (Ferri et al., 2013).

Supervised Injectable Opioid Agonist Therapy

siOAT has been demonstrated to be efficacious in treating people who have severe OUD that has not been well managed by other medications. The treatment is administered under strictly monitored, medically supervised conditions, typically via injection of diacetylmorphine—i.e., pharmaceutical-grade heroin—or of hydromorphone (Drug Policy Alliance, 2016), another opioid currently approved as an analgesic. Evidence demonstrates that among people who have previously been unsuccessful on methadone maintenance therapy, siOAT can significantly improve treatment retention while reducing the use of illicit opioids (Strang et al., 2015). Several countries have carried out studies with mixed results (Fischer et al., 2007). For example, a randomized controlled trial conducted in Canada found that injectable hydromorphone was as effective as injectable diacetylmorphine and had similar treatment outcomes for people with severe OUD (Oviedo-Joekes et al., 2016). Modeling suggests that over a patient's lifetime, siOAT with hydromorphone may provide greater benefit to patients at a lower lifetime cost than methadone maintenance therapy alone (Bansback et al., 2018). Despite this encouraging evidence and the opportunity it represents to engage more people with severe, treatment-

[3] Public Law 63-223, 38 Stat. 785.

resistant OUD in care, siOAT remains unavailable in the United States because it is hampered by political and regulatory barriers (Oviedo-Joekes et al., 2016). However, the growing interest in this modality may lead to the development of better oral, intranasal, or inhalable formulations that could circumvent the stigma associated with injectable opioid medications, even when administered under medical supervision (Klous et al., 2005).

Cannabinoids

Emerging evidence suggests that cannabinoids might be useful as a component of treatment for OUD. "Medical marijuana" has received significant attention because many OUD patients consume recreational marijuana either as a reward substitution in attempts to reduce overdose risk (because cannabis has low mortality risk) or to alleviate anxiety symptoms during opioid withdrawal (Wiese and Wilson-Poe, 2018). Consistently, results from the National Survey on Drug Use and Health (2008 to 2013) indicate that cannabis use in the general population is associated with reduced risk of past year opioid abuse in those with a history of illicit opioid use (Pisano et al., 2017). However, epidemiological evidence (National Epidemiologic Survey on Alcohol and Related Conditions) also suggests an increased risk of prescription opioid misuse and OUD with cannabis use (Olfson et al., 2018), and tetrahydrocannabinol (THC), the psychoactive component of cannabis, has been demonstrated in preclinical models to enhance opioid sensitivity (Ellgren et al., 2007), raising concerns about the potential of THC (and THC-rich medical marijuana strains) to be a viable treatment option for OUD. Dronabinol is an FDA-approved THC analog that has been studied as a treatment for opioid withdrawal, but it had modest efficacy and induced several side effects including tachycardia (Lofwall et al., 2015). More research is needed to compare the effectiveness of dronabinol or other cannabinoids (such as Sativex, a cannabis-based oral spray) to treatment with methadone, buprenorphine, or extended-release naltrexone.

A new line of research has recently focused on the potential of cannabidiol (CBD, a non-intoxicating cannabinoid) to help reduce the risk of opioid relapse by inhibiting drug-seeking behavior (Ren et al., 2009). CBD therapy is also known to relieve some of the psychological and physiological symptoms that are associated with OUD, such as anxiety, insomnia, and pain (Hurd et al., 2015). Unlike medications for OUD that target the endogenous opioid system directly, CBD represents a new way to indirectly affect systems that control opioid-seeking behavior and to support other medications by reducing the craving and anxiety that contribute to relapse (Hurd et al., 2015). CBD has the advantage of negligible abuse potential because it does not produce euphoria, and it has minimal side effects. To date, the data about CBD and its benefits are mostly preclinical. Animal

studies suggest that CBD inhibits trigger-induced heroin-seeking behavior with prolonged effects that may last for weeks, even after relapse (Ren et al., 2009). Pilot studies with humans have demonstrated that CBD is safe to co-administer with the potent injectable opioid fentanyl (Manini et al., 2015), that CBD can induce a decrease in craving for heroin that persists for up to 1 week, and that CBD can reduce anxiety.

Vaccination

Vaccination against opioids to prevent OUD and its consequences is a relatively new avenue of research. Such vaccines work by causing a person's body to create its own antibody response to a specific opioid, thus blocking the psychoactive effects of that opioid in the brain if it is ingested (Bremer et al., 2017). Because mu-opioid receptors are required in order to develop compulsive opioid-taking behavior, it is hypothesized that people will not develop OUD if opioids do not reach the brain. Given that in people with OUD it is common to use more than one type of opioid, the vaccine would need to be effective for the different forms (e.g., fentanyl, heroin). A major drawback is that in order to be effective, vaccines may also inhibit the effects of opioids for critical pain relief or palliative care treatments (Olson and Janda, 2018). Another concern is that a vaccine may also interfere with the use of naloxone as an overdose reversal medication (Raleigh et al., 2017). In addition, ethical considerations may outweigh the prophylactic benefit of vaccination in high-risk populations. Such cases might include offering vaccination as an alternative to incarceration or parents seeking to vaccinate their children against future drug use before they can give consent (Shen et al., 2011). Finally, vaccines do not treat the underlying psychosocial or behavioral correlates of OUD and therefore could lead to the unintended consequence of developing another type of substance use disorder.

Further Research on the Neurobiology of Addiction

Additional research on the neurobiology of addiction and opioid signaling will be needed to advance the development of new medications. Current treatment options target only the opioid reward pathway, but new treatment options targeting other neural systems related to craving, negative affect, and cognitive control will expand our understanding of addiction and therapeutic interventions (Koob and Volkow, 2010). For instance, new mu-opioid receptor agonists that are biased toward specific downstream signaling pathways—and thus do not mediate the rewarding effects of opioids—could result in medications with lower misuse potential. Developing novel, non-opioid treatments that can help to relieve short- and long-term opioid withdrawal symptoms and cravings would require

in-depth research into the interaction of the opioid systems with cellular and molecular mechanisms within discrete neural circuits that maintain long-term maladaptive processes and regulate opioid-seeking behavior. The development of such novel treatments has the potential to facilitate treatment induction, to improve retention in care, and to lengthen remission.

BEHAVIORAL THERAPY IN CONJUNCTION WITH MEDICATIONS

Behavioral interventions are often used in conjunction with medications in treating OUD, for two primary reasons. The first is to target a broad range of problems and issues not addressed by the medications themselves (e.g., comorbid psychiatric symptoms, concurrent use of other drugs, the need for social support, HIV risk behaviors, behavioral changes, motivation). The second is to address limitations associated with each form of medication (e.g., high attrition rates). See Box 2-2 for a description of different types of behavioral interventions that have been used with medication-based treatment for OUD. However, the evidence about the efficacy of different behavioral interventions used to complement each of the FDA-approved medications is limited to date, and the evidence that has been reported is mixed. Interpreting the outcomes is complicated by

BOX 2-2
Types of Behavioral Interventions

The empirically supported behavioral therapies that have been evaluated in the context of medication-based treatment for OUD include (1) contingency management approaches, which provide tangible reinforcement for behaviors such as adherence and submission of drug-free urine specimens (Dugosh et al., 2016); (2) cognitive behavioral approaches, which teach skills and strategies intended to improve control over urges to use and to improve decision-making and problem-solving skills (Carroll and Weiss, 2017); and (3) structured family therapy approaches, which attempt to recruit family support for adherence and retention (Carroll and Onken, 2005).

Behavioral therapies that have not yet been rigorously evaluated in the context of medication-based treatment for OUD include motivational interviewing (McHugh et al., 2010), which attempts to build the individual's own internal motivation for change; acceptance and commitment therapy (Ramsey et al., 2016; Stotts et al., 2009); 12-step facilitation to reduce cocaine use in individuals maintained on methadone (Carroll et al., 2012); mindfulness-based approaches (Zullig et al., 2018); dialectical behavioral therapy (Dimeff and Linehan, 2008); and other ancillary approaches such as yoga (Lander et al., 2017) and acupuncture (Baker and Chang, 2016). While evaluations of some of these approaches are ongoing, the number of studies is too small to draw firm conclusions.

differences in the outcomes targeted in most studies—that is, retention in treatment and reducing opioid use versus addressing comorbid problems such as other drug use, psychosocial functioning, and HIV risk behaviors.

It is generally accepted that the best outcomes are typically achieved through a combination of pharmacological and behavioral therapies (NIDA, 2018), but there is evidence that some individuals may respond adequately to medications plus medical management alone (e.g., evaluation of medication safety and adherence, monitoring, or advice by the prescribing provider) (Gruber et al., 2008; McLellan et al., 1993; Schwartz et al., 2007, 2012; Weiss et al., 2011; Yancovitz et al., 1991). Given the resource limitations and the lack of empirical evidence about specific behavioral interventions to improve outcomes from medications for OUD, some have argued that clinicians should not be dissuaded from initiating medications for OUD simply because evidence-based behavioral therapies are not available (beyond medical management with monitoring) (Schwartz, 2016). At the same time, while medications to treat OUD prevent death and stabilize patients so that their comorbid psychiatric, medical, and social problems can be identified and addressed, these medications alone do not address the many complex problems that many individuals with OUD may have. Therefore, it is critical to take individual differences into account and select a treatment plan that is best suited to each patient's needs (Carroll and Onken, 2005). Provision of behavioral interventions can and often do occur in the medical management encounter with the prescriber.

Methadone Treatment Combined with Behavioral Interventions

There is robust evidence that contingency management interventions that reward positive behaviors are effective as behavioral adjuncts to methadone treatment. Furthermore, treatment retention improves when patients are permitted to take the medication home. Take-home medication privileges based on drug-free urine specimens have consistently been shown to reduce illicit drug use (Carroll and Onken, 2005), as have incentive programs using vouchers for goods and services to reward time without drug use (Silverman et al., 1996). Low-cost contingency management interventions (in which individuals earn chances to win prizes rather than earn vouchers) have also demonstrated efficacy and may be suitable and more acceptable for resource-constrained treatment settings (Petry and Martin, 2002).

A systematic review examining 14 recent studies found that, with the exception of contingency management, behavioral therapies themselves do not generally improve retention or reduce opioid use in individuals with OUD receiving methadone treatment (Dugosh et al., 2016). However, results from studies that target "secondary" outcomes such as psychosocial

functioning and other drug use generally support the addition of behavioral interventions. Studies have also examined the effectiveness of the counseling that patients are required to receive in real-world OTPs. The results do not demonstrate differences in treatment retention or opioid use among patients who were randomized to receive little or no interaction with OTP drug counselors versus patients who received the federally mandated level of counseling (Gruber et al., 2008; Schwartz et al., 2006, 2012; Yancovitz et al., 1991). When considered in aggregate, these data suggest that the psychosocial supports required at OTPs should be recalibrated.

Buprenorphine Treatment Combined with Behavioral Interventions

A systematic review of eight randomized controlled trials found mixed results with respect to the additional benefit of adding behavioral intervention to medical management in office-based buprenorphine treatment (Carroll and Weiss, 2017). Four of the trials found no additional benefit of behavioral therapy interventions that included varying the intensity of medical management (Fiellin et al., 2006; Ling et al., 2013; Weiss et al., 2011); cognitive behavioral therapy (Fiellin et al., 2014; Ling et al., 2013); contingency management with or without cognitive behavioral therapy (Ling et al., 2013); and medical management plus drug counseling (Weiss et al., 2011). The other four randomized controlled trials demonstrated some additional benefit of adding the behavioral interventions, particularly those that used contingency management as the intervention (Bickel et al., 2008; Christensen et al., 2014; Miotto et al., 2012; Schottenfeld et al., 2005). The authors suggested that research design may have played a role in these opposing outcomes. The four trials that reported no additional benefit of behavioral intervention all featured relatively intensive medical management in addition to the behavioral intervention under evaluation, while three of the four positive studies did not offer structured medical management.

To date, no trials have evaluated the efficacy of buprenorphine alone, without medical management, as the minimal standard of care. Thus, there are no data on the number or types of individuals who may respond to buprenorphine without medical management and monitoring (Carroll and Weiss, 2017). Another recent systematic review examined group-based therapy for OUD combined with buprenorphine, finding multiple methodological problems with most of the studies (e.g., small sample size, varying theoretical focus, weak control groups) that make it difficult to draw conclusions regarding efficacy (Sokol et al., 2018). However, some evidence suggests that patients with other comorbid addictions or psychiatric disorders have better outcomes when behavioral interventions are included in their treatment regimens (Arias and Kranzler, 2008; Kelly and Daley, 2013).

Naltrexone Treatment Combined with Behavioral Interventions

A recent systematic review found that relatively few robust studies meeting the criteria for inclusion had investigated behavioral interventions used with naltrexone (Dugosh et al., 2016). Most of the high-quality studies involved the use of contingency management to improve adherence to naltrexone and the submission of opioid-free urine specimens. Several trials have evaluated contingency management strategies with oral—not extended-release—naltrexone (Carroll et al., 2002; Dunn et al., 2013; Nunes et al., 2006; Preston et al., 1999), finding positive effects on treatment retention, attendance, and compliance in the short term, but poor treatment retention in the longer term. Two studies of injectable extended-release naltrexone in conjunction with contingency management found that the combination was effective in improving treatment retention and in increasing the number of naltrexone injections received (DeFulio et al., 2012; Everly et al., 2011).

KNOWLEDGE GAPS AND ADDITIONAL RESEARCH NEEDED ON THE ROLE OF BEHAVIORAL INTERVENTIONS WITH MEDICATIONS IN TREATMENT FOR OUD

Apart from contingency management, it is difficult to say which behavioral intervention will be most effective with a given medication or a given outcome in a given patient. Relatively few studies have investigated the comparative or differential effectiveness of different types of behavioral interventions in treating OUD at different points in the continuum of care, among different populations, or in different treatment settings (Dugosh et al., 2016). Given the mortality benefit of the medications, more research into behavioral interventions that result in improved treatment adherence is critical; behavioral techniques also have promising potential to assist patients in achieving good long-term functional outcomes. Investigating behavioral techniques to facilitate improvements in psychiatric, legal, interpersonal, and occupational functioning may support sustained remission (Carroll and Weiss, 2017). Other techniques may reduce HIV and HCV risk behaviors, regardless of other treatment outcomes (Edelman et al., 2014; Meade et al., 2010).

Another knowledge gap in OUD behavioral treatment innovations pertains to the provision of peer support to enhance treatment. Peer support is "the process of giving and receiving nonprofessional, nonclinical assistance from individuals with similar conditions or circumstances to achieve long-term recovery from psychiatric, alcohol, and/or other drug-related problems" (Tracy and Wallace, 2016, p. 143). Peer-based recovery support has a long history in addiction treatment and was advocated for by Dole and

Nyswander, who developed the methadone maintenance treatment model for OUD (White, 2009). Peer support groups to supplement treatment for addiction have promising potential to increase treatment engagement and to reduce substance use and risk behaviors for infectious disease transmission, but more rigorous studies are needed (Tracy and Wallace, 2016). Peer providers with lived experience related to addiction may be able to contribute positively to other people's OUD treatments and to help address the vast workforce shortages in behavioral health. However, the inclusion of peer providers gives rise to important concerns about their training, certification, methodological consistency across programs, opportunities for career advancement, and fair compensation. Despite the high degree of public investment in these programs nationally, there are no data from well-controlled trials evaluating peer support. More research is needed to explore how peer providers may be able to support OUD treatment and to establish the effect size of such interventions (Chapman et al., 2018; Reif et al., 2014).

Conclusion 2: U.S. Food and Drug Administration–approved medications to treat opioid use disorder are effective and save lives.

FDA-approved medications to treat OUD—methadone, buprenorphine, and extended-release naltrexone—are effective and save lives. The most appropriate medication varies by individual and may change over time. To stem the opioid crisis, it is critical for all FDA-approved options to be available for all people with OUD. At the same time, as with all medical disorders, continued research on new medications, approaches, and formulations that will expand the options for patients is needed.

Conclusion 3:
Long-term retention on medication for opioid use disorder is associated with improved outcomes.

There is evidence that retention on medication for the long term is associated with improved outcomes and that discontinuing medication often leads to relapse and overdose. There is insufficient evidence regarding how the medications compare over the long term.

Conclusion 4:
Lack of availability or utilization of behavioral interventions is not a sufficient justification to withhold medications to treat opioid use disorder.

Behavioral interventions, in addition to medical management, do not appear to be necessary as treatment in all cases. Some people may do well with medication and medical management alone. However, evidence-based behavioral interventions can be useful in engaging people with OUD in treatment, retaining them in treatment, improving outcomes, and helping them resume a healthy functioning life. There is inadequate evidence about which behavioral interventions provided in conjunction with medications for OUD are most helpful for which patients, including evidence on how effective peer support is; more research is needed to address this knowledge deficit.

REFERENCES

Ali, S., B. Tahir, S. Jabeen, and M. Malik. 2017. Methadone treatment of opiate addiction: A systematic review of comparative studies. *Innovations in Clinical Neuroscience* 14(7–8):8–19.

Alves, P., and A. Winstock. 2011. Patients' knowledge about treatment for opiate dependence. *Psychiatrist* 35:448–453.

Arias, A. J., and H. R. Kranzler. 2008. Treatment of co-occurring alcohol and other drug use disorders. *Alcohol Research & Health* 31(2):155–167.

ASAM (American Society of Addiction Medicine). 2016. *Nurse practitioners and physician assistants prescribing buprenorphine*. https://www.asam.org/resources/practice-resources/nurse-practitioners-and-physician-assistants-prescribing-buprenorphine (accessed January 15, 2019).

Baker, T. E., and G. Chang. 2016. The use of auricular acupuncture in opioid use disorder: A systematic literature review. *American Journal on Addictions* 25(8):592–602.

Bansback, N., D. Guh, E. Oviedo-Joekes, S. Brissette, S. Harrison, A. Janmohamed, M. Krausz, S. MacDonald, D. C. Marsh, M. T. Schechter, and A. H. Anis. 2018. Cost-effectiveness of hydromorphone for severe opioid use disorder: Findings from the SALOME randomized clinical trial. *Addiction* 113(7):1264–1273.

Bao, Y. P., Z. M. Liu, D. H. Epstein, C. Du, J. Shi, and L. Lu. 2009. A meta-analysis of retention in methadone maintenance by dose and dosing strategy. *American Journal of Drug and Alcohol Abuse* 35(1):28–33.

Bart, G. 2012. Maintenance medication for opiate addiction: The foundation of recovery. *Journal of Addictive Diseases* 31(3):207–225.

Bart, G., Q. Wang, J. S. Hodges, C. Nolan, and G. Carlson. 2012. Superior methadone treatment outcome in Hmong compared with non-Hmong patients. *Journal of Substance Abuse Treatment* 43(3):269–275.

Bart, G., Z. Wyman, Q. Wang, J. S. Hodges, R. Karim, and B. A. Bart. 2017. Methadone and the QTc interval: Paucity of clinically significant factors in a retrospective cohort. *Journal of Addiction Medicine* 11(6):489–493.

Bawor, M., H. Bami, B. B. Dennis, C. Plater, A. Worster, M. Varenbut, J. Daiter, D. C. Marsh, M. Steiner, R. Anglin, M. Coote, G. Pare, L. Thabane, and Z. Samaan. 2015. Testosterone suppression in opioid users: A systematic review and meta-analysis. *Drug and Alcohol Dependence* 149:1–9.

Beck, T., C. Haasen, U. Verthein, S. Walcher, C. Schuler, M. Backmund, C. Ruckes, and J. Reimer. 2014. Maintenance treatment for opioid dependence with slow-release oral morphine: A randomized cross-over, non-inferiority study versus methadone. *Addiction* 109(4):617–626.

Bickel, W. K., L. A. Marsch, A. R. Buchhalter, and G. J. Badger. 2008. Computerized behavior therapy for opioid-dependent outpatients: A randomized controlled trial. *Experimental and Clinical Psychopharmacology* 16(2):132–143.

Binswanger, I. A., and J. M. Glanz. 2018. Potential risk window for opioid overdose related to treatment with extended-release injectable naltrexone. *Drug Safety* 41(10):979–980.

Bird, S. M., A. McAuley, S. Perry, and C. Hunter. 2016. Effectiveness of Scotland's National Naloxone Programme for reducing opioid-related deaths: A before (2006–10) versus after (2011–13) comparison. *Addiction* 111(5):883–891.

Bremer, P. T., J. E. Schlosburg, M. L. Banks, F. F. Steele, B. Zhou, J. L. Poklis, and K. D. Janda. 2017. Development of a clinically viable heroin vaccine. *Journal of the American Chemical Society* 139(25):8601–8611.

Bukten, A., S. Skurtveit, M. Gossop, H. Waal, P. Stangeland, I. Havnes, and T. Clausen. 2012. Engagement with opioid maintenance treatment and reductions in crime: A longitudinal national cohort study. *Addiction* 107(2):393–399.

Carroll, K. M., and L. S. Onken. 2005. Behavioral therapies for drug abuse. *The American Journal of Psychiatry* 162(8):1452–1460.

Carroll, K. M., and R. D. Weiss. 2017. The role of behavioral interventions in buprenorphine maintenance treatment: A review. *The American Journal of Psychiatry* 174(8):738–747.

Carroll, K. M., R. Sinha, C. Nich, T. Babuscio, and B. J. Rounsaville. 2002. Contingency management to enhance naltrexone treatment of opioid dependence: A randomized clinical trial of reinforcement magnitude. *Experimental and Clinical Psychopharmacology* 10(1):54–63.

Carroll, K. M., C. Nich, J. M. Shi, D. Eagan, and S. A. Ball. 2012. Efficacy of disulfiram and twelve step facilitation in cocaine-dependent individuals maintained on methadone: A randomized placebo-controlled trial. *Drug and Alcohol Dependence* 126(1–2):224–231.

Chapman, S. A., L. K. Blash, K. Mayer, and J. Spetz. 2018. Emerging roles for peer providers in mental health and substance use disorders. *American Journal of Preventive Medicine* 54(6S3):S267–S274.

Christensen, D. R., R. D. Landes, L. Jackson, L. A. Marsch, M. J. Mancino, M. P. Chopra, and W. K. Bickel. 2014. Adding an internet-delivered treatment to an efficacious treatment package for opioid dependence. *Journal of Consulting and Clinical Psychology* 82(6):964–972.

Cicero, T. J., M. S. Ellis, H. L. Surratt, and S. P. Kurtz. 2014. Factors contributing to the rise of buprenorphine misuse: 2008–2013. *Drug and Alcohol Dependence* 142:98–104.

Coffin, P. O., E. Behar, C. Rowe, G. M. Santos, D. Coffa, M. Bald, and E. Vittinghoff. 2016. Nonrandomized intervention study of naloxone coprescription for primary care patients receiving long-term opioid therapy for pain. *Annals of Internal Medicine* 165(4):245–252.

Connery, H. S. 2015. Medication-assisted treatment of opioid use disorder: Review of the evidence and future directions. *Harvard Review of Psychiatry* 23(2):63–75.

CRS (Congressional Research Service). 2018. *Opioid treatment programs and related federal regulations*. https://fas.org/sgp/crs/misc/IF10219.pdf (accessed February 9, 2019).

Dahan, A., A. Yassen, R. Romberg, E. Sarton, L. Teppema, E. Olofsen, and M. Danhof. 2006. Buprenorphine induces ceiling in respiratory depression but not in analgesia. *British Journal of Anaesthesia* 96(5):627–632.

Davis, C., and D. Carr. 2017. State legal innovations to encourage naloxone dispensing. *Journal of the American Pharmaceutical Association (2003)* 57(2S):S180–S184.

Dean, A. J., J. B. Saunders, R. T. Jones, R. M. Young, J. P. Connor, and B. R. Lawford. 2006. Does naltrexone treatment lead to depression? Findings from a randomized controlled trial in subjects with opioid dependence. *Journal of Psychiatry and Neuroscience* 31(1):38–45.

DeFulio, A., J. J. Everly, J.-M. S. Leoutsakos, A. Umbricht, M. Fingerhood, G. E. Bigelow, and K. Silverman. 2012. Employment-based reinforcement of adherence to an FDA-approved extended release formulation of naltrexone in opioid-dependent adults: A randomized controlled trial. *Drug and Alcohol Dependence* 120(1–3):48–54.

Degenhardt, L., D. Randall, W. Hall, M. Law, T. Butler, and L. Burns. 2009. Mortality among clients of a state-wide opioid pharmacotherapy program over 20 years: Risk factors and lives saved. *Drug and Alcohol Dependence* 105(1):9–15.

Degenhardt, L., C. Bucello, B. Mathers, C. Briegleb, H. Ali, M. Hickman, and J. McLaren. 2011. Mortality among regular or dependent users of heroin and other opioids: A systematic review and meta-analysis of cohort studies. *Addiction* 106(1):32–51.

Degenhardt, L., S. Larney, J. Kimber, M. Farrell, and W. Hall. 2015. Excess mortality among opioid-using patients treated with oral naltrexone in Australia. *Drug and Alcohol Review* 34(1):90–96.

Dimeff, L. A., and M. M. Linehan. 2008. Dialectical behavior therapy for substance abusers. *Addiction Science & Clinical Practice* 4(2):39–47.

Doughty, B. D. Morgenson, and T. Brooks. 2019. Lofexifine: a newly FDA-approved, nonopioid treatment for opioid withdrawal. *Annals of Pharmacotherapy*. doi: 10.1177/1060028019828954.

Drug Policy Alliance. 2016. *Heroin-assisted treatment (HAT)*. https://www.drugpolicy.org/sites/default/files/DPA%20Fact%20Sheet_Heroin-Assisted%20Treatment_(Feb.%202016).pdf (accessed February 9, 2019).

Dugosh, K., A. Abraham, B. Seymour, K. McLoyd, M. Chalk, and D. Festinger. 2016. A systematic review on the use of psychosocial interventions in conjunction with medications for the treatment of opioid addiction. *Journal of Addiction Medicine* 10(2):93–103.

Dunn, K. E., A. Defulio, J. J. Everly, W. D. Donlin, W. M. Aklin, P. A. Nuzzo, J. M. Leoutsakos, A. Umbricht, M. Fingerhood, G. E. Bigelow, and K. Silverman. 2013. Employment-based reinforcement of adherence to oral naltrexone treatment in unemployed injection drug users. *Experimental and Clinical Psychopharmacology* 21(1):74–83.

Dunn, K., A. DeFulio, J. J. Everly, W. D. Donlin, W. M. Aklin, P. A. Nuzzo, J. M. Leoutsakos, A. Umbricht, M. Fingerhood, G. E. Bigelow, and K. Silverman. 2015. Employment-based reinforcement of adherence to oral naltrexone in unemployed injection drug users: 12-month outcomes. *Psychology of Addictive Behaviors* 29(2):270–276.

Eastwood, B., J. Strang, and J. Marsden. 2017. Effectiveness of treatment for opioid use disorder: A national, five-year, prospective, observational study in England. *Drug and Alcohol Dependence* 176:139–147.

Edelman, E. J., T. Chantarat, S. Caffrey, A. Chaudhry, P. G. O'Connor, L. Weiss, D. A. Fiellin, and L. E. Fiellin. 2014. The impact of buprenorphine/naloxone treatment on HIV risk behaviors among HIV-infected, opioid-dependent patients. *Drug and Alcohol Dependence* 139:79–85.

Ellgren, M., S. M. Spano, and Y. L. Hurd. 2007. Adolescent cannabis exposure alters opiate intake and opioid limbic neuronal populations in adult rats. *Neuropsychopharmacology* 32(3):607–615.

Everly, J. J., A. DeFulio, M. N. Koffarnus, J.-M. S. Leoutsakos, W. D. Donlin, W. M. Aklin, A. Umbricht, M. Fingerhood, G. E. Bigelow, and K. Silverman. 2011. Employment-based reinforcement of adherence to depot naltrexone in unemployed opioid-dependent adults: A randomized controlled trial. *Addiction (Abingdon, England)* 106(7):1309–1318.

Faggiano, F., F. Vigna-Taglianti, E. Versino, and P. Lemma. 2003. Methadone maintenance at different dosages for opioid dependence. *Cochrane Database of Systematic Reviews* 2003(3):CD002208.

Fareed, A., D. Patil, K. Scheinberg, R. Blackinton Gale, S. Vayalapalli, J. Casarella, and K. Drexler. 2013. Comparison of qtc interval prolongation for patients in methadone versus buprenorphine maintenance treatment: A 5-year follow-up. *Journal of Addictive Diseases* 32(3):244–251.

FDA (U.S. Food and Drug Administration). 2017. *FDA urges caution about withholding opioid addiction medications from patients taking benzodiazepines or CNS depressants: Careful medication management can reduce risks*. www.fda.gov/Drugs/DrugSafety/ucm575307.htm (accessed February 9, 2019).

FDA. 2018. *Information about medication-assisted treatment (MAT)*. https://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm600092.htm (accessed December 11, 2018).

Ferri, M., S. Minozzi, A. Bo, and L. Amato. 2013. Slow-release oral morphine as maintenance therapy for opioid dependence. *Cochrane Database of Systematic Reviews* 2013(6):CD009879.

Fiellin, D. A., M. V. Pantalon, M. C. Chawarski, B. A. Moore, L. E. Sullivan, P. G. O'Connor, and R. S. Schottenfeld. 2006. Counseling plus buprenorphine-naloxone maintenance therapy for opioid dependence. *New England Journal of Medicine* 355(4):365–374.

Fiellin, D. A., R. S. Schottenfeld, C. J. Cutter, B. A. Moore, D. T. Barry, and P. G. O'Connor. 2014. Primary care-based buprenorphine taper vs. maintenance therapy for prescription opioid dependence: A randomized clinical trial. *JAMA Internal Medicine* 174(12):1947–1954.

Fischer, B., E. Oviedo-Joekes, P. Blanken, C. Haasen, J. Rehm, M. T. Schechter, J. Strang, and W. van den Brink. 2007. Heroin-assisted treatment (HAT) a decade later: A brief update on science and politics. *Journal of Urban Health* 84(4):552–562.

Fishman, M., C. Tirado, D. Alam, K. Gullo, T. Clinch, and C. W. Gorodetzky. 2018. Safety and efficacy of lofexidine for medically managed opioid withdrawal: A randomized controlled clinical trial. *Journal of Addiction Medicine*. doi: 10.1097/ADM.0000000000000474.

Fudala, P. J., T. P. Bridge, S. Herbert, W. O. Williford, C. N. Chiang, K. Jones, J. Collins, D. Raisch, P. Casadonte, R. J. Goldsmith, W. Ling, U. Malkerneker, L. McNicholas, J. Renner, S. Stine, D. Tusel, and the Buprenorphine/Naloxone Collaborative Study Group. 2003. Office-based treatment of opiate addiction with a sublingual-tablet formulation of buprenorphine and naloxone. *New England Journal of Medicine* 349(10):949–958.

Gearing, F. R. 1974. Methadone maintenance treatment five years later: Where are they now? *American Journal of Public Health* 64(Suppl 12):44–50.

Goldstein, A., and J. Herrera. 1995. Heroin addicts and methadone treatment in Albuquerque: A 22-year follow-up. *Drug and Alcohol Dependence* 40(2):139–150.

Gossop, M., J. Marsden, D. Stewart, and T. Kidd. 2003. The National Treatment Outcome Research Study (NTORS): 4–5 year follow-up results. *Addiction* 98(3):291–303.

Gowing, L., M. F. Farrell, R. Bornemann, L. E. Sullivan, and R. Ali. 2011. Oral substitution treatment of injecting opioid users for prevention of HIV infection. *Cochrane Database of Systematic Reviews* 2011(8):CD004145.

Green, T. C., E. F. Dauria, J. Bratberg, C. S. Davis, and A. Y. Walley. 2015. Orienting patients to greater opioid safety: Models of community pharmacy-based naloxone. *Harm Reduction Journal* 12:25.

Green, T. C., J. Clarke, L. Brinkley-Rubinstein, B. D. L. Marshall, N. Alexander-Scott, R. Boss, and J. D. Rich. 2018. Postincarceration fatal overdoses after implementing medications for addiction treatment in a statewide correctional system. *JAMA Psychiatry* 75(4):405–407.

Gruber, V. A., K. L. Delucchi, A. Kielstein, and S. L. Batki. 2008. A randomized trial of 6-month methadone maintenance with standard or minimal counseling versus 21-day methadone detoxification. *Drug and Alcohol Dependence* 94(1–3):199–206.

HHS (U.S. Department of Health and Human Services). 2018. *Naloxone: The opioid reversal drug that saves lives. 2018*. https://www.hhs.gov/opioids/sites/default/files/2018-12/naloxone-coprescribing-guidance.pdf (accessed January 15, 2019).

Hser, Y., V. Hoffman, C. E. Grella, and M. D. Anglin. 2001. A 33-year follow-up of narcotics addicts. *Archives of General Psychiatry* 58:503–508.

Hser, Y. I., A. J. Saxon, D. Huang, A. Hasson, C. Thomas, M. Hillhouse, P. Jacobs, C. Teruya, P. McLaughlin, K. Wiest, A. Cohen, and W. Ling. 2014. Treatment retention among patients randomized to buprenorphine/naloxone compared to methadone in a multi-site trial. *Addiction* 109(1):79–87.

Hurd, Y. L., M. Yoon, A. F. Manini, S. Hernandez, R. Olmedo, M. Ostman, and D. Jutras-Aswad. 2015. Early phase in the development of cannabidiol as a treatment for addiction: Opioid relapse takes initial center stage. *Neurotherapeutics* 12(4):807–815.

Jarvis, B. P., A. F. Holtyn, S. Subramaniam, D. A. Tompkins, E. A. Oga, G. E. Bigelow, and K. Silverman. 2018. Extended-release injectable naltrexone for opioid use disorder: A systematic review. *Addiction* 113(7):1188–1209.

Jegu, J., A. Gallini, P. Soler, J. L. Montastruc, and M. Lapeyre-Mestre. 2011. Slow-release oral morphine for opioid maintenance treatment: A systematic review. *British Journal of Clinical Pharmacology* 71(6):832–843.

Jones, C. M., M. Campopiano, G. Baldwin, and E. McCance-Katz. 2015. National and state treatment need and capacity for opioid agonist medication-assisted treatment. *American Journal of Public Health* 105(8):e55–e63.

Kakko, J., K. D. Svanborg, M. J. Kreek, and M. Heilig. 2003. 1-year retention and social function after buprenorphine-assisted relapse prevention treatment for heroin dependence in Sweden: A randomised, placebo-controlled trial. *Lancet* 361(9358):662–668.

Kampman, K., and M. Jarvis. 2015. American Society of Addiction Medicine (ASAM) national practice guideline for the use of medications in the treatment of addiction involving opioid use. *Journal of Addiction Medicine* 9(5):358–367.

Kelly, T. M., and D. C. Daley. 2013. Integrated treatment of substance use and psychiatric disorders. *Social Work in Public Health* 28(3–4):388–406.

Kelty, E., and G. Hulse. 2017. Fatal and non-fatal opioid overdose in opioid dependent patients treated with methadone, buprenorphine, or implant naltrexone. *International Journal of Drug Policy* 46:54–60.

Kimber, J., S. Larney, M. Hickman, D. Randall, and L. Degenhardt. 2015. Mortality risk of opioid substitution therapy with methadone versus buprenorphine: A retrospective cohort study. *Lancet Psychiatry* 2(10):901–908.

Kleber, H. D. 2007. Pharmacologic treatments for opioid dependence: Detoxification and maintenance options. *Dialogues in Clinical Neuroscience* 9(4):455–470.

Klous, M. G., W. Van den Brink, J. M. Van Ree, and J. H. Beijnen. 2005. Development of pharmaceutical heroin preparations for medical co-prescription to opioid dependent patients. *Drug and Alcohol Dependence* 80(3):283–295.

Koob, G. F., and N. D. Volkow. 2010. Neurocircuitry of addiction. *Neuropsychopharmacology* 35(1):217–238.

Kreek, M. J. 2000. Methadone-related opioid agonist pharmacotherapy for heroin addiction. History, recent molecular and neurochemical research and future in mainstream medicine. *Annals of the New York Academy of Sciences* 909:186–216.

Krupitsky, E., E. V. Nunes, W. Ling, A. Illeperuma, D. R. Gastfriend, and B. L. Silverman. 2011. Injectable extended-release naltrexone for opioid dependence: A double-blind, placebo-controlled, multicentre randomised trial. *Lancet* 377:1506–1513.

Lander, L., K. Chiasson Downs, M. Andrew, G. Rader, S. Dohar, and K. Waibogha. 2017. Yoga as an adjunctive intervention to medication-assisted treatment withbuprenorphine + naloxone. *Journal of Addiction Research and Therapy* 8(6). doi: 10.4172/155-6105.1000354.

Larochelle, M. R., N. M. Cocoros, J. Popovic, E. C. Dee, C. Kornegay, J. Ju, and J. A. Racoosin. 2017. Opioid tolerance and urine drug testing among initiates of extended-release or long-acting opioids in Food and Drug Administration's Sentinel System. *Journal of Opioid Management* 13(5):315–327.

Lee, J. D., P. D. Friedmann, T. W. Kinlock, E. V. Nunes, T. Y. Boney, R. A. Hoskinson, Jr., D. Wilson, R. McDonald, J. Rotrosen, M. N. Gourevitch, M. Gordon, M. Fishman, D. T. Chen, R. J. Bonnie, J. W. Cornish, S. M. Murphy, and C. P. O'Brien. 2016. Extended-release naltrexone to prevent opioid relapse in criminal justice offenders. *New England Journal of Medicine* 374:1232–1242.

Lee, J. D., E. V. Nunes, Jr., P. Novo, K. Bachrach, G. L. Bailey, S. Bhatt, S. Farkas, M. Fishman, P. Gauthier, C. C. Hodgkins, J. King, R. Lindblad, D. Liu, A. G. Matthews, J. May, K. M. Peavy, S. Ross, D. Salazar, P. Schkolnik, D. Shmueli-Blumberg, D. Stablein, G. Subramaniam, and J. Rotrosen. 2018. Comparative effectiveness of extended-release naltrexone versus buprenorphine-naloxone for opioid relapse prevention (x:Bot): A multicentre, open-label, randomised controlled trial. *Lancet* 391(10118):309–318.

Ling, W., M. Hillhouse, A. Ang, J. Jenkins, and J. Fahey. 2013. Comparison of behavioral treatment conditions in buprenorphine maintenance. *Addiction* 108(10):1788–1798.

Lofwall, M. R., S. Babalonis, P. A. Nuzzo, S. C. Elayi, and S. L. Walsh. 2016. Opioid withdrawal suppression efficacy of oral dronabinol in opioid dependent humans. *Drug and Alcohol Dependence* 164:143–150.

MacArthur, G. J., S. Minozzi, N. Martin, P. Vickerman, S. Deren, J. Bruneau, L. Degenhardt, and M. Hickman. 2012. Opiate substitution treatment and HIV transmission in people who inject drugs: Systematic review and meta-analysis. *BMJ* 345:e5945.

Maglione, M. A., L. Raaen, C. Chen, G. Azhar, N. Shahidinia, M. M. Shen, E. Maksabedian, R. M. Shanman, S. Newberry, and S. Hempel. 2018. Effects of medication assisted treatment (MAT) for opioid use disorder on functional outcomes: A systematic review. *Journal of Substance Abuse Treatment* 89:28–51.

Manhapra, A., R. Rosenheck, and D. A. Fiellin. 2017. Opioid substitution treatment is linked to reduced risk of death in opioid use disorder. *BMJ* 357:j1947.

Manini, A. F., G. Yiannoulos, M. M. Bergamaschi, S. Hernandez, R. Olmedo, A. J. Barnes, G. Winkel, R. Sinha, D. Jutras-Aswad, M. A. Huestis, and Y. L. Hurd. 2015. Safety and pharmacokinetics of oral cannabidiol when administered concomitantly with intravenous fentanyl in humans. *Journal of Addiction Medicine* 9(3):204–210.

Mattick, R. P., C. Breen, J. Kimber, and M. Davoli. 2009. Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. *Cochrane Database of Systematic Reviews* 2009(3):CD002209.

Mattick, R. P., C. Breen, J. Kimber, and M. Davoli. 2014. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *Cochrane Database of Systematic Reviews* 2014(2):CD002207.

McHugh, R. K., B. A. Hearon, and M. W. Otto. 2010. Cognitive-behavioral therapy for substance use disorders. *Psychiatric Clinics of North America* 33(3):511–525.

McLellan, A. T., I. O. Arndt, D. S. Metzger, G. E. Woody, and C. P. O'Brien. 1993. The effects of psychosocial services in substance abuse treatment. *JAMA* 269(15):1953–1959.

Meade, C. S., R. D. Weiss, G. M. Fitzmaurice, S. A. Poole, G. A. Subramaniam, A. A. Patkar, H. S. Connery, and G. E. Woody. 2010. HIV risk behavior in treatment-seeking opioid-dependent youth: Results from a NIDA clinical trials network multisite study. *Journal of Acquired Immune Deficiency Syndromes* 55(1):65–72.

Minozzi, S., L. Amato, S. Vecchi, M. Davoli, U. Kirchmayer, and A. Verster. 2011. Oral naltrexone maintenance treatment for opioid dependence. *Cochrane Database of Systematic Reviews* 2011(4):CD001333.

Miotto, K., M. Hillhouse, R. Donovick, J. Cunningham-Rathner, C. Charuvastra, M. Torrington, A. E. Esagoff, and W. Ling. 2012. Comparison of buprenorphine treatment for opioid dependence in 3 settings. *Journal of Addiction Medicine* 6(1):68–76.

Morgan, J. R., B. R. Schackman, J. A. Leff, B. P. Linas, and A. Y. Walley. 2018. Injectable naltrexone, oral naltrexone, and buprenorphine utilization and discontinuation among individuals treated for opioid use disorder in a United States commercially insured population. *Journal of Substance Abuse Treatment* 85:90–96.

NIDA (National Institute on Drug Abuse). 2018. *Principles of drug addiction treatment: A research-based guide, 3rd ed*. https://www.drugabuse.gov/publications/principles-drug-addiction-treatment-research-based-guide-third-edition (accessed February 9, 2019).

NIH (National Institutes of Health). 1998. Effective medical treatment of opiate addiction. National Consensus Development Panel on Effective Medical Treatment of Opiate Addiction. *Journal of the American Medical Association* 280:1936–1943.

Nunes, E. V., J. L. Rothenberg, M. A. Sullivan, K. M. Carpenter, and H. D. Kleber. 2006. Behavioral therapy to augment oral naltrexone for opioid dependence: A ceiling on effectiveness? *American Journal of Drug and Alcohol Abuse* 32(4):503–517.

O'Connor, P. G., and T. R. Kosten. 1998. Rapid and ultrarapid opioid detoxification techniques. *Journal of the American Medical Association* 279(3):229–234.

Olfson, M., M. M. Wall, S. M. Liu, and C. Blanco. 2018. Cannabis use and risk of prescription opioid use disorder in the United States. *The American Journal of Psychiatry* 175(1):47–53.

Olson, M. E., and K. D. Janda. 2018. Vaccines to combat the opioid crisis: Vaccines that prevent opioids and other substances of abuse from entering the brain could effectively treat addiction and abuse. *EMBO Reports* 19(1):5–9.

Oviedo-Joekes, E., D. Guh, S. Brissette, K. Marchand, S. MacDonald, K. Lock, S. Harrison, A. Janmohamed, A. H. Anis, M. Krausz, D. C. Marsh, and M. T. Schechter. 2016. Hydromorphone compared with diacetylmorphine for long-term opioid dependence: A randomized clinical trial. *JAMA Psychiatry* 73(5):447–455.

Peles, E., S. Schreiber, V. Rados, and M. Adelson. 2011. Low risk for hepatitis C seroconversion in methadone maintenance treatment. *Journal of Addiction Medicine* 5(3):214–220.

Petry, N. M., and B. Martin. 2002. Low-cost contingency management for treating cocaine- and opioid-abusing methadone patients. *Journal of Consulting and Clinical Psychology* 70(2):398–405.

Pierce, M., S. M. Bird, M. Hickman, J. Marsden, G. Dunn, A. Jones, and T. Millar. 2016. Impact of treatment for opioid dependence on fatal drug-related poisoning: A national cohort study in England. *Addiction* 111(2):298–308.

Pisano, V. D., N. P. Putnam, H. M. Kramer, K. J. Franciotti, J. H. Halpern, and S. C. Holden. 2017. The association of psychedelic use and opioid use disorders among illicit users in the United States. *Journal of Psychopharmacology* 31(5):606–613.

Ponizovsky, A. M., and A. Grinshpoon. 2007. Quality of life among heroin users on buprenorphine versus methadone maintenance. *American Journal of Drug and Alcohol Abuse* 33(5):631–642.

Preston, K. L., K. Silverman, A. Umbricht, A. DeJesus, I. D. Montoya, and C. R. Schuster. 1999. Improvement in naltrexone treatment compliance with contingency management. *Drug and Alcohol Dependence* 54(2):127–135.

Raleigh, M. D., S. J. Peterson, M. Laudenbach, F. Baruffaldi, F. I. Carroll, S. D. Comer, H. A. Navarro, T. L. Langston, S. P. Runyon, S. Winston, M. Pravetoni, and P. R. Pentel. 2017. Safety and efficacy of an oxycodone vaccine: Addressing some of the unique considerations posed by opioid abuse. *PLOS ONE* 12(12):e0184876.

Ramsey, S. E., D. Rounsaville, R. Hoskinson, T. W. Park, E. G. Ames, V. D. Neirinckx, and P. Friedmann. 2016. The need for psychosocial interventions to facilitate the transition to extended-release naltrexone (XR-NTX) treatment for opioid dependence: A concise review of the literature. *Substance Abuse: Research and Treatment* 10:65–68.

Reif, S., L. Braude, D. R. Lyman, R. H. Dougherty, A. S. Daniels, S. S. Ghose, O. Salim, and M. E. Delphin-Rittmon. 2014. Peer recovery support for individuals with substance use disorders: Assessing the evidence. *Psychiatric Services* 65(7):853–861.

Ren, Y., J. Whittard, A. Higuera-Matas, C. V. Morris, and Y. L. Hurd. 2009. Cannabidiol, a nonpsychotropic component of cannabis, inhibits cue-induced heroin seeking and normalizes discrete mesolimbic neuronal disturbances. *Journal of Neuroscience* 29(47):14764–14769.

Schottenfeld, R. S., M. C. Chawarski, J. R. Pakes, M. V. Pantalon, K. M. Carroll, and T. R. Kosten. 2005. Methadone versus buprenorphine with contingency management or performance feedback for cocaine and opioid dependence. *The American Journal of Psychiatry* 162(2):340–349.

Schuckit, M. A. 2016. Treatment of opioid-use disorders. *New England Journal of Medicine* 375(4):357–368.

Schwartz, R. P. 2016. When added to opioid agonist treatment, psychosocial interventions do not further reduce the use of illicit opioids: A comment on Dugosh et al. *Journal of Addiction Medicine* 10(4):283–285.

Schwartz, R. P., D. A. Highfield, J. H. Jaffe, J. V. Brady, C. B. Butler, C. O. Rouse, J. M. Callaman, K. E. O'Grady, and R. J. Battjes. 2006. A randomized controlled trial of interim methadone maintenance. *Archives of General Psychiatry* 63(1):102–109.

Schwartz, R. P., J. H. Jaffe, D. A. Highfield, J. M. Callaman, and K. E. O'Grady. 2007. A randomized controlled trial of interim methadone maintenance: 10-month follow-up. *Drug and Alcohol Dependence* 86(1):30–36.

Schwartz, R. P., J. H. Jaffe, K. E. O'Grady, T. W. Kinlock, M. S. Gordon, S. M. Kelly, M. E. Wilson, and A. Ahmed. 2009. Interim methadone treatment: Impact on arrests. *Drug and Alcohol Dependency* 103(3):148–154.

Schwartz, R. P., S. M. Kelly, K. E. O'Grady, D. Gandhi, and J. H. Jaffe. 2011. Interim methadone treatment compared to standard methadone treatment: 4-month findings. *Journal of Substance Abuse and Treatment* 41(1):21–29.

Schwartz, R. P., S. M. Kelly, K. E. O'Grady, D. Gandhi, and J. H. Jaffe. 2012. Randomized trial of standard methadone treatment compared to initiating methadone without counseling: 12-month findings. *Addiction (Abingdon, England)* 107(5):943–952.

Schwartz, R. P., J. Gryczynski, K. E. O'Grady, J. M. Sharfstein, G. Warren, Y. Olsen, S. G. Mitchell, and J. H. Jaffe. 2013. Opioid agonist treatments and heroin overdose deaths in Baltimore, Maryland, 1995–2009. *American Journal of Public Health* 103(5):917–922.

Shen, X., F. M. Orson, and T. R. Kosten. 2011. Anti-addiction vaccines. *F1000 Med Reports* 3:20.

Silverman, K., C. J. Wong, S. T. Higgins, R. K. Brooner, I. D. Montoya, C. Contoreggi, A. Umbricht-Schneiter, C. R. Schuster, and K. L. Preston. 1996. Increasing opiate abstinence through voucher-based reinforcement therapy. *Drug and Alcohol Dependence* 41(2):157–165.

Simpson, D. D., G. W. Joe, and S. A. Bracy. 1982. Six-year follow-up of opioid addicts after admission to treatment. *Archives of General Psychiatry* 39(11):1318–1323.

Sokol, R., A. E. LaVertu, D. Morrill, C. Albanese, and Z. Schuman-Olivier. 2018. Group-based treatment of opioid use disorder with buprenorphine: A systematic review. *Journal of Substance Abuse Treatment* 84:78–87.

Sordo, L., G. Barrio, M. J. Bravo, B. I. Indave, L. Degenhardt, L. Wiessing, M. Ferri, and R. Pastor-Barriuso. 2017. Mortality risk during and after opioid substitution treatment: Systematic review and meta-analysis of cohort studies. *BMJ* 357:j1550.

Stotts, A. L., A. Masuda, and K. Wilson. 2009. Using acceptance and commitment therapy during methadone dose reduction: Rationale, treatment description, and a case report. *Cognitive and Behavioral Practice* 16(2):205–213.

Strang, J., T. Groshkova, A. Uchtenhagen, W. Van den Brink, C. Haasen, M. Schechter, N. Lintzeris, J. Bell, A. Pirona, E. Oviedo-Joekes, R. Simon, and N. Metrebian. 2015. Heroin on trial: Systematic review and meta-analysis of randomised trials of diamorphine-prescribing as treatment for refractory heroin addiction. *British Journal of Psychiatry* 207(1):5–14.

Sullivan, M., A. Bisaga, M. Pavlicova, C. J. Choi, K. Mishlen, K. M. Carpenter, F. R. Levin, E. Dakwar, J. J. Mariani, and E. V. Nunes. 2017. Long-acting injectable naltrexone induction: A randomized trial of outpatient opioid detoxification with naltrexone versus buprenorphine. *The American Journal of Psychiatry* 174(5):459–467.

Sun, H.-M., X.-Y. Li, E. P. F. Chow, T. Li, Y. Xian, Y.-H. Lu, T. Tian, X. Zhuang, and L. Zhang. 2015. Methadone maintenance treatment programme reduces criminal activity and improves social well-being of drug users in China: A systematic review and meta-analysis. *BMJ Open* 5(1):e005997.

Tanum, L., K. K. Solli, Z. E. Latif, J. S. Benth, A. Opheim, K. Sharma-Haase, P. Krajci, and N. Kunoe. 2017. Effectiveness of injectable extended-release naltrexone vs daily buprenorphine-naloxone for opioid dependence: A randomized clinical noninferiority trial. *JAMA Psychiatry* 74:1197–205.

Thomas, C. P., C. A. Fullerton, M. Kim, L. Montejano, D. R. Lyman, R. H. Dougherty, A. S. Daniels, S. S. Ghose, and M. E. Delphin-Rittmon. 2014. Medication-assisted treatment with buprenorphine: Assessing the evidence. *Psychiatric Services* 65(2):158–170.

Timko, C., N. R. Schultz, M. A. Cucciare, L. Vittorio, and C. Garrison-Diehn. 2016. Retention in medication-assisted treatment for opiate dependence: A systematic review. *Journal of Addictive Diseases* 35(1):22–35.

Tracy, K., and S. P. Wallace. 2016. Benefits of peer support groups in the treatment of addiction. *Substance Abuse and Rehabilitation* 7:143–154.

Uebelacker, L. A., G. Bailey, D. Herman, B. Anderson, and M. Stein. 2016. Patients' beliefs about medications are associated with stated preference for methadone, buprenorphine, naltrexone, or no medication-assisted therapy following inpatient opioid detoxification. *Journal of Substance Abuse Treatment* 66:48–53.

Vermont Department of Health. 2018. *Opioid use disorder treatment census and wait list (as of September 2018)*. http://www.healthvermont.gov/sites/default/files/documents/pdf/ADAP_OpioidUseDisorderTreatmentCensusandWaitList.pdf (accessed January 15, 2019).

Weiss, R. D., J. S. Potter, D. A. Fiellin, M. Byrne, H. S. Connery, W. Dickinson, J. Gardin, M. L. Griffin, M. N. Gourevitch, D. L. Haller, A. L. Hasson, Z. Huang, P. Jacobs, A. S. Kosinski, R. Lindblad, E. F. McCance-Katz, S. E. Provost, J. Selzer, E. C. Somoza, S. C. Sonne, and W. Ling. 2011. Adjunctive counseling during brief and extended buprenorphine-naloxone treatment for prescription opioid dependence: A 2-phase randomized controlled trial. *Archives of General Psychiatry* 68(12):1238–1246.

Wheeler, E., T. S. Jones, M. K Gilbert, and P. J. Davidson. 2015. Opioid overdose prevention programs providing naloxone to laypersons—United States, 2014. *Morbidity and Mortality Weekly Report* 64(23):631–635.

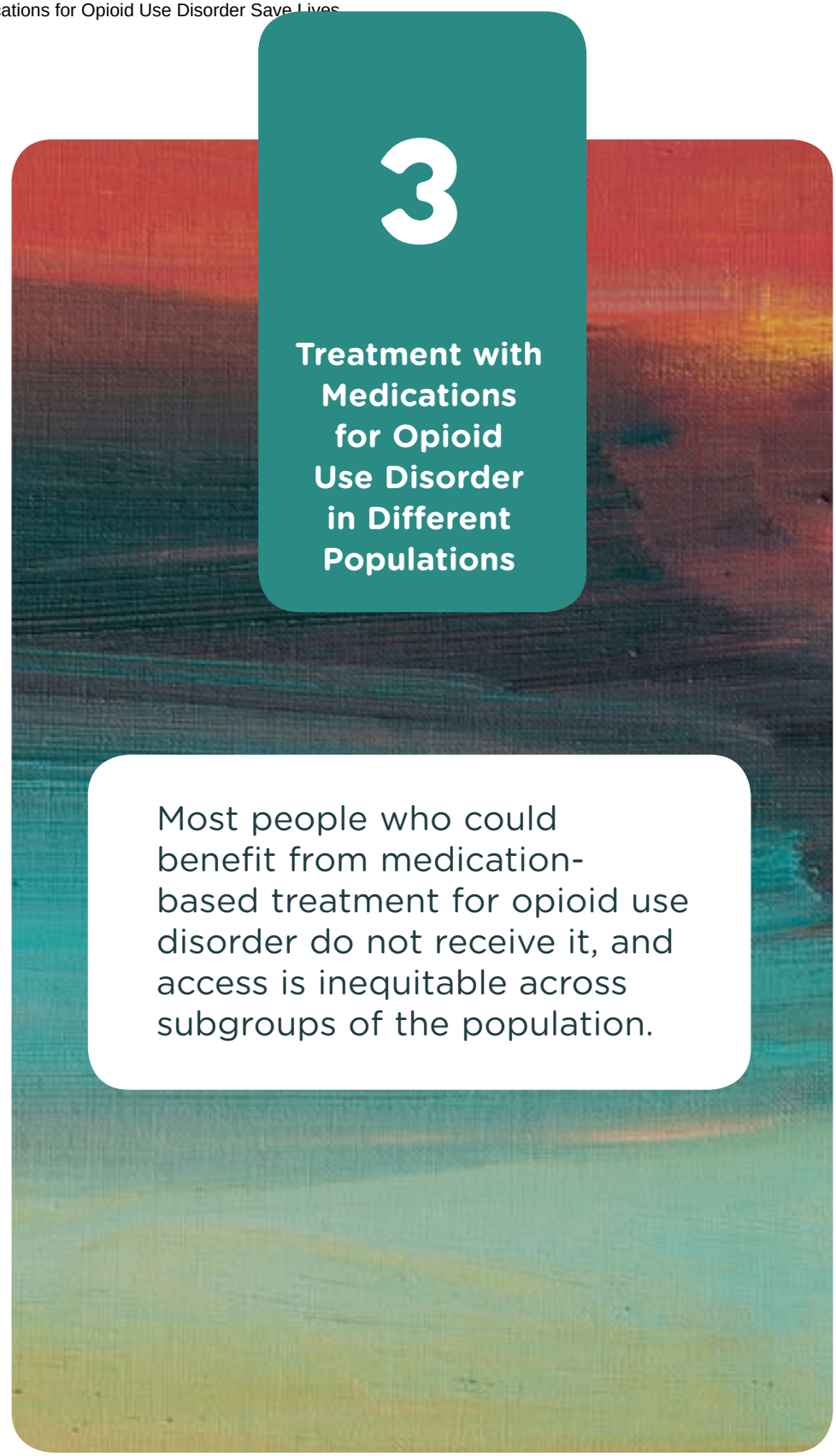
White, W. L. 2009. Peer-based addiction recovery support: History, therapy, practice, and scientific evaluation. *Counselor* 10(5):54–59. http://www.williamwhitepapers.com/pr/2009PeerRecoverySupportMonographExecutiveSummary.pdf (accessed February 18, 2019).

Wiese, B., and A. R. Wilson-Poe. 2018. Emerging evidence for cannabis' role in opioid use disorder. *Cannabis and Cannabinoid Research* 3(1):179–189.

Woody, G. E., D. Bruce, P. T. Korthuis, S. Chhatre, S. Poole, M. Hillhouse, P. Jacobs, J. Sorensen, A. J. Saxon, D. Metzger, and W. Ling. 2014. HIV risk reduction with buprenorphine-naloxone or methadone: Findings from a randomized trial. *Journal of Acquired Immune Deficiency Syndromes* 66(3):288–293.

Yancovitz, S. R., D. C. Des Jarlais, N. P. Peyser, E. Drew, P. Friedmann, H. L. Trigg, and J. W. Robinson. 1991. A randomized trial of an interim methadone maintenance clinic. *American Journal of Public Health* 81(9):1185–1191.

Zullig, K. J., L. R. Lander, S. Sloan, M. R. Brumage, G. R. Hobbs, and L. Faulkenberry. 2018. Mindfulness-based relapse prevention with individuals receiving medication-assisted outpatient treatment for opioid use disorder. *Mindfulness* 9(2):423–429.



3

Treatment with Medications for Opioid Use Disorder in Different Populations

Most people who could benefit from medication-based treatment for opioid use disorder do not receive it, and access is inequitable across subgroups of the population.

Medications are effective treatments for opioid use disorder (OUD) across a broad range of populations that have been studied, but access to these medications varies widely and is inequitable both across patient groups and across treatment settings. This chapter examines the evidence about the provision of OUD medications within the United States to different populations, including children and adolescents; older persons; different sexes and genders; pregnant women; sexual minorities; individuals with comorbidities; racial and ethnic minorities; people of low socioeconomic status; and rural and urban populations. However, more and better data are needed to track the rates of people with OUD receiving medication nationally and within subsets of the population (see Box 3-1).

MEDICATION-BASED TREATMENT FOR OUD ACROSS THE LIFE COURSE

Adolescents and Young Adults

Opioid use has escalated among the U.S. population under 25 years old, with rates of OUD increasing six-fold between 2001 and 2014 among this age group (Hadland et al., 2017). This population can be segmented into adolescents between 12 and 17 years old and young adults between 18 and 25 years old. The 2017 National Survey on Drug Use and Health

BOX 3-1
National Estimates of People with Opioid Use Disorder (OUD) Receiving Medication-Based Treatment

We do not currently have rigorously collected data to allow for national estimates of the number of people with OUD receiving medication-based treatment, their retention rates in treatment, or their treatment outcomes. These kinds of data are critical as a basis for tracking shifts in treatment over time and in how treatment rates vary regionally or across population subgroups. Moreover, better national estimates on medication-based treatment rates are also needed to track and evaluate efforts to expand the availability of medications. One possible example is the Cascade of Care framework, derived from the strategy to scale up access to antiretroviral treatment of human immunodeficiency virus (HIV) (Gardner et al., 2011). As applied to systematically measuring progress through treatment of OUD, the Cascade of Care model articulates five stages: (1) accurate diagnosis (detection), (2) linkage to care of those diagnosed, (3) initiation of medications for those entering care, (4) retention on medication-based treatment for at least 6 months, and (5) stable remission (Socias et al., 2016; Williams et al., 2017, 2018).

(NSDUH) indicates that 3.1 percent of adolescents had misused opioids in the previous year, with 0.1 percent having used heroin and 3.1 percent having misused prescription opioids. Among persons between 18 and 25 years of age, around 7.3 percent had misused opioids in the previous year, with 0.7 percent using heroin and 7.1 percent misusing prescription opioids (SAMHSA, 2018). A study of administrative databases in Massachusetts found that the prevalence of OUD was significantly higher than the national prevalence estimated by NSDUH; it was increasing most rapidly in that state among people aged between 11 and 25 years (Barocas et al., 2018). According to the American Academy of Pediatrics (AAP), OUD is the leading cause of morbidity and mortality among adolescents and young adults in the United States (Committee on Substance Use and Prevention, 2016). However, national prevalence data suggest that opioid use among adolescents is decreasing, with the annual prevalence of past-year, non-heroin, narcotic use among 12th grade students decreasing from 9.5 percent in 2003 to 3.4 percent in 2018 and past-year use of heroin decreasing from 1.5 percent in 2000 to 0.4 percent in 2018 among the same age group. This suggests that prevention strategies may be having a positive effect, but it may also suggest that adolescents who use opioids may not be frequent presenters to the health care system.

Adolescents with OUD have unique treatment needs and may have complex pre-morbid issues. Given the developmental changes that people undergo during adolescence, treatment strategies designed for adults may not be appropriate for those who are not yet 18 (Center for Substance Abuse Treatment, 2006). Risk factors for substance use and disorders among adolescents include genetic predisposition, peer influence, a family history of substance use, emotional or affective disorders, troubled family relations, school problems, and a history of victimization (Weinberg et al., 1998; Whitesell et al., 2013). Brain development is also a factor in both vulnerability and susceptibility within this age group. The maturing adolescent brain has been shown to be vulnerable to the acute effects of drugs and substance use during adolescence, which increase a person's risk of developing a chronic substance use disorder (SUD) later in life (Casey et al., 2008). Moreover, substance use can delay normal development during adolescence (Center for Substance Abuse Treatment, 2006). People with OUD in this age group likely need a comprehensive assessment to determine whether adolescent or adult treatment strategies would be most appropriate.

Methadone and naltrexone have not been well studied in adolescents with OUD due to federal restrictions, but the limited data available do support the use of medication-based treatment in this population. Buprenorphine treatment in adolescents with OUD has an existing evidence base. In a clinical trial, adolescent patients who received buprenorphine maintenance treatment plus counseling after medically supervised with-

drawal were more likely to remain in treatment after 3 months than patients who only received counseling after withdrawal (Woody et al., 2008). A retrospective review of long-term treatment outcomes for buprenorphine–naloxone treatment among adolescents with OUD found that treatment retention helps to promote long-term remission (Matson et al., 2014). A multistate retrospective cohort study found that adolescents and young adults who received medication for OUD (buprenorphine, naltrexone, or methadone) within 3 months of diagnosis were more likely to stay in treatment than those who received behavioral therapy alone (Hadland et al., 2018a). Compared to adults, however, adolescents tend to have lower rates of treatment retention (Dreifuss et al., 2013; Marsch et al., 2005; Schuman-Olivier et al., 2014). Creating innovative, developmentally appropriate treatment strategies tailored to this age group could help to improve treatment outcomes (Committee on Substance Use and Prevention, 2016). A key knowledge gap in this area is the dearth of randomized controlled trials specifically focused on adolescents' use of and retention in medication-based treatment.

Access to medication-based treatment for adolescents and young adults remains vastly inadequate in the United States (Committee on Substance Use and Prevention, 2016; Knudsen et al., 2011). In 2016 the AAP officially recommended that pediatricians consider offering medication-based treatment to adolescents and young adults with OUD, but it remains highly restricted and widely underused (Committee on Substance Use and Prevention, 2016). The exact number of adolescents with OUD who receive medications is unknown. However, a study using the 2013 Treatment Episode Data Set found that among adolescents being treated for OUD in publicly funded programs, only 2.4 percent of those being treated for heroin use and just 0.4 percent of those being treated for prescription opioid misuse had received medication (Feder et al., 2017). A 2018 study reported that among youths (between 13 and 22 years of age) with OUD in the United States, just one-quarter of those who were commercially insured and less than 5 percent of those on Medicaid received medication (Hadland et al., 2018a).

Multiple factors may contribute to adolescents' lack of access to medication-based treatment; these factors may not necessarily apply to young adults. For example, adolescents who are living at home or covered under a parent's insurance plan may not wish to disclose their drug use. Parents may be unwilling to provide consent for their minor children to receive medication-based treatment for OUD due to the stigma surrounding the medications. If adolescents and their parents do seek medication-based treatment for OUD, their options are very limited. Naltrexone is only approved for individuals 18 years and older, and federal regulations prohibit most opioid treatment programs (OTPs) from providing methadone to patients younger than 18 years. Buprenorphine is approved by the U.S.

Food and Drug Administration (FDA) for treating patients 16 years and older, but restrictive policies and resource constraints have severely limited its availability (Chang et al., 2018; Feder et al., 2017; Hadland et al., 2018b). As a result of these regulatory restrictions, many adolescents with OUD undergo medically supervised withdrawal with behavioral therapy alone, without the benefit of evidence-based medications.

Older Persons

OUD is on the rise among older populations (SAMHSA, 2017). According to the 2017 NSDUH, 4.6 million adults 50 years or older had had an SUD in the past year (SAMHSA, 2018). Little is known about the mortality and morbidity of OUD in this group or about models of care that can comprehensively address their complex health issues. Due to their age, the use of multiple medications, including sedatives, and a higher likelihood of concurrent chronic illness, older adults are particularly vulnerable to certain consequences of OUD such as delirium, memory loss, suicide, falls and fractures, drug–drug interactions, and drug–disease interactions. One study found that adults over 50 years of age with OUD were more likely to die from any cause and from HIV- or liver-related deaths than their peers without OUD (Larney et al., 2015). Furthermore, OUD can present differently in older populations and requires different types of treatment to restore functional status. However, treatment outcomes for older adults are often equivalent to or better than treatment outcomes among younger people (Clay, 2010).

SEX-RELATED DIFFERENCES IN MEDICATION-BASED TREATMENT FOR OUD

According to data from the NSDUH, 5.15 million females (3.7 percent) had past-year opioid misuse, compared to 6.25 million males (4.7 percent). Almost 60 million females aged 12 and older (35.7 percent) had used pain relievers in the past year, compared to 40.8 million males (30.9 percent). Little is known about sex-related differences in the risk, chronicity, and treatment of OUD (Mazure and Fiellin, 2018). For example, in a recent Cochrane review of the use of buprenorphine for OUD, the majority of the combined sample reviewed was male, and none of the 26 randomized, controlled trials reported results by sex, so the effects of sex/gender could not be assessed (Gowing et al., 2017). According to the NSDUH (2005–2013), OUD in the United States is more common in males (57 percent) than females (42 percent) (Wu et al., 2016), although recent trends over time suggest that drug use among women is increasing at a faster rate than among males (Cicero et al., 2014). Further studies are needed to better

understand the treatment of postpartum women, the treatment of women who are not pregnant, and sex-specific differences in treatment outcomes (Gowing et al., 2017).

Several lines of evidence underscore the need to consider sex and gender in OUD. Women report lower rates of OUD and are more likely to report both widespread and localized pain conditions, including fibromyalgia, migraine, and chronic headache (Bartley and Fillingim, 2013; Serdarevic et al., 2017). Women are more likely than men to have first used prescribed opioids, which they obtain at a higher rate than men (Cicero et al., 2009; Fillingim et al., 2009; Manubay et al., 2015; McHugh et al., 2013). Following an initial opioid exposure, women may transition from initial use to problematic opioid use faster than men (Back et al., 2011; Hernandez-Avila et al., 2004). Among treatment-seeking individuals with OUD, women have more comorbid psychiatric disorders than men, including major depressive and anxiety disorders as well as posttraumatic stress disorder (Grella et al., 2009; McHugh et al., 2013) and psychological distress (Back et al., 2010; Bawor et al., 2015; Manubay et al., 2015; McHugh et al., 2013); men have more comorbid alcohol and other SUDs and legal problems. The analgesic and withdrawal-suppressing effects of opioids are sex sensitive and likely influenced by fluctuations in the female sex hormones estradiol and progesterone (Doyle and Murphy, 2018; Elliott et al., 2006; Loyd and Murphy, 2009; Peckham and Traynor, 2006; Santoro et al., 2017a,b). Finally, some evidence suggests that women may feel more comfortable receiving treatment for OUD in certain settings, such as primary care (Jones and Fiellin, 2007).

Sex-related differences in the treatment of OUD remain largely underexplored, but existing evidence suggests that there are distinct sex-based predictors of methadone treatment response, retention, and outcomes (Levine et al., 2015). Little is known about sex-related differences with respect to dose patterns and length of treatment (Frimpong et al., 2017). An analysis of a nationally representative survey of drug treatment programs found that in methadone treatment programs, an increasing proportion of female patients was associated with a lower proportion of patients in treatment for longer than 1 year (Frimpong et al., 2017), suggesting that some female patients may receive less effective treatment for OUD. A study of all OUD patients enrolled in publicly funded OTPs licensed to dispense methadone in California (2006–2010) found sex differences in mortality risk. Concurrent opioid and methamphetamine/cocaine use increased the mortality risk among women, but it decreased the risk among men; men were more likely than women to benefit from reduced mortality risk through interventions to reduce overdose risk after a period of time without opioid use (Evans et al., 2015).

Clinical and social characteristics also differ between women and men with OUD. A study of methadone treatment programs found that, com-

pared to men, women tended to be admitted at a younger age and after a shorter duration of opioid use (Adelson et al., 2018). Compared with men, women who have SUDs are more likely to have been victims of violent childhood and domestic abuse (Ouimette et al., 2000) and to have co-occurring psychiatric disorders (Zilberman et al., 2003). Although parents who receive medication for OUD are more likely to retain custody of their children (Hall et al., 2016), the fear of losing custody can discourage women from seeking treatment, as can the fear of retribution from a violent domestic partner (Center for Substance Abuse Treatment, 2006). Because women tend to be the primary caregivers, childcare issues can also pose barriers to entering and remaining in treatment for OUD. Women with OUD who have children may benefit from enhanced services in addition to medication-based treatment to address their social service needs (Marsh et al., 2000). Because histories of emotional, physical, and sexual trauma are prominent in the narratives of women who use drugs (Torchalla et al., 2015), many SUD treatment providers have adopted trauma-informed care and integrated treatment, with important subsequent improvements in mental health and service use (Messina et al., 2014). Women-centered treatment for SUDs may also include the provision of family counseling, child care, residential care for clients' children, transportation assistance, domestic violence services, care options for pregnant women, and comprehensive mental health care; however, such treatment services are declining in availability (Terplan et al., 2015).

PREGNANT WOMEN

Pregnant women with OUD are another population with unique treatment needs that are largely unmet. Among pregnant women in the United States, the prevalence of OUD quadrupled from 0.15 to 0.65 percent between 1999 and 2014, with large variability across states (Haight et al., 2018). Overdose is one of the leading causes of maternal deaths in the United States, with the risk of overdose increasing as the postpartum period progresses (Schiff et al., 2018). A retrospective cohort study looking at women with OUD in Massachusetts found that the rate of overdose was lowest in the third trimester (at 3.3/100,000 person-days) and increased after delivery, with the highest rates 7 to 12 months postdelivery (12.3/100,000 person-days) (Schiff et al., 2018). Pregnant women with untreated OUD are up to six times more likely than other women to have maternal complications, including low birthweight and fetal distress, while neonatal complications among babies born to mothers with OUD range from neonatal abstinence syndrome and neurobehavioral problems to a 74-fold increase in sudden infant death syndrome (Minozzi et al., 2013).

Treatment Outcomes for Pregnant Women and Their Infants

Both methadone and buprenorphine are recommended for treating OUD in pregnancy to improve outcomes for the woman and the newborn (Kotelchuck et al., 2017). The efficacy and safety of methadone treatment for OUD in pregnant women is long established. In women who receive methadone treatment during pregnancy, the outcomes for their infants (e.g., likelihood of the pregnancy going to term and healthy birth weight) are similar or within normal ranges compared with infants who were not exposed to methadone (Kaltenbach and Finnegan, 1984; Stimmel and Adamsons, 1976). Methadone has traditionally been the primary treatment for pregnant women with OUD, but more recent research indicates that buprenorphine treatment has potential benefits compared with methadone in this population. A randomized controlled trial of methadone versus buprenorphine in pregnant women with OUD found that neonates exposed to buprenorphine required 89 percent less morphine, had shorter hospital stays, and received a shorter duration of treatment for neonatal abstinence syndrome relative to pregnant women treated with methadone (Jones et al., 2010). Other outcomes and adverse events were similar between the two groups (Jones et al., 2010).

A comparison of OUD treatments for pregnant women across seven studies found no significant differences in maternal outcomes, neonatal outcomes, or serious adverse outcomes for buprenorphine–naloxone compared with buprenorphine alone, methadone maintenance, or methadone-assisted withdrawal (Lund et al., 2013). The safety of extended-release naltrexone has not yet been established for pregnant women (Connery, 2015) and currently naltrexone is not recommended for the treatment of OUD in women who are pregnant.

Despite the sound evidence base, most pregnant women with OUD do not receive any treatment with medications (Metz et al., 2018; Terplan et al., 2015). Among women who do receive treatment during pregnancy, many fall out of treatment during the postpartum period (sometimes called the "fourth trimester") due to gaps in insurance coverage and other systemic barriers. The proportion of pregnant women with OUD admitted to publicly funded treatment programs has increased from about 17 to 41 percent since the mid-1990s, but the proportion of those women in treatment who receive medication to treat their OUD has remained static—at roughly 50 percent—with significant regional, demographic, and treatment facility variability (Short et al., 2018). Although the rates of OUD among pregnant women have sharply increased, many women cannot access appropriate services (Terplan et al., 2015). One study that looked at the National Survey of Substance Abuse Treatment Services of 13,000 SUD facilities found that the proportion offering services for pregnant and postpartum

women declined from 19 percent in 2002 to 15 percent in 2009 (Terplan et al., 2015). An integrated approach with close collaboration between OUD treatment providers and prenatal providers has been described as the "gold standard" for care (Klaman et al., 2017). Further research is needed to better understand the effects of medication-based treatment in pregnant women and postpartum women as well as to investigate interventions that could help to increase treatment retention.

SEXUAL MINORITIES

Little is known about opioid use and medication-based treatment for OUD among sexual minority groups, including lesbian, gay, and bisexual adolescents and adults. Sexual minorities accounted for just 2 percent of the sample of approximately 35,000 adults in the 2004–2005 U.S. National Epidemiologic Survey on Alcohol and Related Conditions. Respondents with SUDs who were sexual minorities were less likely to receive OUD treatment than the sexual majority population; sexual minority respondents—particularly women—were more likely to have lifetime SUDs. Sexual minorities also tended to have more extensive family histories of substance misuse (Duncan et al., 2019). According to the 2015 NSDUH, respondents identifying as bisexual were more than 1.5 times more likely to report past-month and past-year opioid misuse than those identifying as heterosexual. A nationally representative sample of U.S. adults revealed disparities in opioid misuse and OUD across different sexual orientations (Duncan et al., 2019). No data exist on the proportion of sexual minorities with OUD who receive medication-based treatment, which is an important area for further research. For sexual minority populations with OUD, for example, treatment programs could be delivered through a trauma-informed approach to care that integrates primary care with behavioral health and specifically addresses the stressors experienced by sexual minorities (Girouard et al., 2019).

INDIVIDUALS WITH OUD AND OTHER MORBIDITIES

Comorbidities are common among people with OUD, particularly co-occurring mental health disorders, other SUDs, and long-term chronic pain. Infectious diseases have also reached epidemic proportions among people with OUD in some communities, driven by the increase in injection drug use. Complex interactions among comorbid conditions can affect treatment strategies and outcomes, and people with OUD and comorbidities would likely benefit from much more integrated care strategies than those that now prevail.

Populations with Co-occurring Mental Health Disorders

Up to 40 percent of people receiving treatment for SUDs may have co-occurring mental health disorders, such as antisocial personality disorder, major depression, or general anxiety (Flynn et al., 1996). According to the NSDUH (2005–2013), 29 percent of people with OUD have had a major depressive episode (Wu et al., 2016). A study of the impact of mental health comorbidities on buprenorphine treatment adherence in patients with an OUD found that 22 percent of patients had comorbid anxiety disorder and about 16 percent had comorbid bipolar disorder (Litz and Leslie, 2017). High rates of attention deficit hyperactivity disorder symptoms have been found among heroin-dependent patients—especially those with severe OUD—who also have higher rates of other comorbid mental health conditions (Lugoboni et al., 2017). Co-occurring mental health disorders appear to be more commonly diagnosed among women than men; they are also more commonly diagnosed among people engaged in the criminal justice system than the general population (Center for Substance Abuse Treatment, 2006; Mbaba et al., 2018).

Comorbid mental health disorders can affect OUD treatment outcomes. Members of this population face unique challenges, making them more likely to drop out of medication-based treatment (Krawczyk et al., 2017b). One study found that patients with bipolar disorder being treated with buprenorphine for comorbid OUD were significantly less likely to adhere to buprenorphine treatment (Litz and Leslie, 2017). Most people with OUD and co-occurring psychiatric disorders do not receive treatment for either problem. Less than half of people with severe mental health and SUDs receive any treatment, and only about 7 percent receive treatment for both disorders (Priester et al., 2016). This may be due in part to their complex treatment needs; for example, they may have interacting symptoms of multiple disorders and compounding social factors such as victimization, poverty, or homelessness. This population tends to have very limited access to evidence-based treatment and poorly coordinated treatment for their co-occurring disorders (Center for Substance Abuse Treatment, 2006; Watkins et al., 2001).

Among people with comorbid mental health disorders, medications to treat OUD have the potential to improve outcomes and reduce the risk of overdose, hospitalization, and emergency department visits (Robertson et al., 2018). A recent study looked at medication-based treatment for adults with schizophrenia, autism spectrum disorder, bipolar disorder, or major depression as well as comorbid moderate to severe OUD. Methadone, buprenorphine, and oral naltrexone were all associated with reductions in the need for inpatient OUD treatment and with improved adherence to medications for the comorbid mental health disorders (Robertson et al.,

2018). A study of methadone treatment among people who use heroin found that depression improves quickly during the first 3 months of treatment, after which it plateaus; depression decreased more rapidly among women and among younger people (Wang et al., 2017).

People with OUD and co-occurring mental health disorders may benefit from integrated, concomitant treatment for their co-occurring disorders, augmented by continuous outreach and support for medication adherence, treatment retention, coordination of care, and accessing social services (Charney et al., 2001; Drake and Mueser, 2000). Ideally, care for the psychiatric comorbidities would be integrated into OUD treatment settings, and the reverse (Krawczyk et al., 2017b).

Populations with Other Substance Use Disorders

According to the NSDUH (2005–2013), 80 percent of individuals with OUD had a co-occurring SUD (Wu et al., 2016). In clinical samples of individuals with OUD, rates of current comorbid SUD range from 13 to 49 percent for alcohol, 20 to 40 percent for stimulant, 28 to 41 percent for cannabis, and 80 to 95 percent for tobacco (Rosic et al., 2017; Strain, 2002). Patients with other SUDs may require special dosing and tolerance considerations when being treated with medication for OUD.

Unhealthy alcohol use can interfere with the treatment for OUD, with heavy drinking often cited by clinicians as a contraindication to medication-based treatment for OUD because both substances may depress respiratory function. However, even heavy alcohol use does not appear to increase the risk of overdose death (Klimas et al., 2018), and FDA released a statement explicitly noting that the use of alcohol or other drugs that depress the central nervous system should not be considered a contraindication to treatment with buprenorphine or methadone (FDA, 2017).

Cocaine and other stimulant use is frequent among individuals in methadone and buprenorphine treatment and has been associated with lower retention and poorer outcomes, although the data are mixed (Kosten et al., 1992; Sullivan et al., 2010). As noted in Chapter 2, contingency management is a behavioral treatment that demonstrated effectiveness in treating stimulant use disorder in patients in methadone treatment (Cunningham et al., 2013; Griffith et al., 2000).

Patients who are receiving medication to treat OUD have disproportionately high rates of tobacco use disorder (Yee et al., 2018). Failing to address tobacco use can negatively affect OUD treatment, and the OUD treatment process provides an opportunity to provide smoking cessation treatment (Mannelli et al., 2013). For example, one study found that patients with OUD retained in office-based buprenorphine treatment were more likely to receive smoking cessation medications than people not

retained in treatment (Nahvi et al., 2014a). A meta-analysis of smoking cessation interventions among patients receiving methadone treatment found that nicotine replacement therapy led to significant reductions in smoking (Yee et al., 2018). Evidence suggests that varenicline can support short-term abstinence from smoking among people with OUD receiving methadone maintenance treatment (Nahvi et al., 2014b). Naltrexone has been studied as a potential treatment to aid in smoking cessation in individuals with OUD, though evidence does not seem to suggest that it has a clinical benefit (David et al., 2006).

Populations with Chronic Pain

Both chronic pain and addiction are conditions driven by neurophysiological processes and shaped by a confluence of genetic and environmental factors (Center for Substance Abuse Treatment, 2012). Studies of people receiving methadone treatment for OUD have found that 37 to 65 percent of patients reported moderate to severe chronic pain (Dhingra et al., 2012; Rosenblum et al., 2003).

Chronic pain might negatively affect drug-use outcomes in people with OUD, although the data are mixed. In one study, people with chronic pain receiving buprenorphine treatment for OUD had similar outcomes to those without chronic pain (Fox et al., 2012). Across several studies of patients on methadone, chronic pain is associated with poor psychosocial and physical function—as it is in the general population—but it is not necessarily associated with a return to use of opioids or other substances (Dennis et al., 2015). The same meta-analysis found no effect of chronic pain on any OUD treatment outcomes for patients maintained on buprenorphine (Dennis et al., 2015). A subsequent trial demonstrated that patients with chronic pain who discontinue buprenorphine are more likely to return to use than patients without chronic pain who discontinue buprenorphine (Worley et al., 2017). Emerging evidence demonstrates improved pain outcomes for patients with chronic pain converted from full agonist opioids to buprenorphine (Daitch et al., 2014; Pade et al., 2012), and future research should compare outcomes across the different OUD medications. Meanwhile, treating OUD in people who have chronic pain remains a clinical challenge, highlighting a critical gap in strategies to manage chronic pain among this population (Delorme et al., 2018).

Populations with Comorbid Infectious Diseases

It is increasingly evident that the ongoing epidemics of OUD, opioid overdose, hepatitis C virus (HCV), and HIV in the United States are linked and warrant combined evidence-based interventions for prevention and

treatment. These would include broad HCV and HIV testing and substance use screening, the provision of medications to treat OUD, and increased population-level HCV treatment (Perlman and Jordan, 2018). A variety of successful models have been described for co-locating the treatment of all three conditions (Rich et al., 2018).

Epidemiological studies reveal that among people who inject drugs in the United States, HIV rates are decreasing and HCV rates are increasing (Schranz et al., 2018). However, rural counties hard hit by the opioid epidemic are experiencing catastrophic increases in HIV transmission as well as HCV (NASEM, 2018). These increases in infectious disease transmission rates are being driven in large part by increases in injection drug use in communities across the country.

Interactions between methadone and older medications for HIV, such as efavirenz, and interactions between buprenorphine and ritonavir-boosted atazanavir may have historically impacted OUD treatment in people living with HIV. However, such interactions are less of a concern with the current first-list antiretroviral therapies, which are regimens containing integrase inhibitors (Gourevitch and Friedland, 2000; McCance-Katz et al., 2007). Methadone and buprenorphine treatment significantly reduce the use of illicit opioids and HIV transmission risk behaviors, such as injection drug use and the sharing of injection equipment (Gowing et al., 2011; Woody et al., 2014). Methadone and buprenorphine also improve HIV viral suppression and adherence to antiretroviral therapy. Extended-release naltrexone has been shown to improve HIV viral suppression in persons with HIV leaving prison (Fanucchi et al., 2019). Co-location of HIV and OUD treatment in primary care or OTPs has been demonstrated to improve treatment outcomes for both conditions (Berg et al., 2011; Low et al., 2016; Lucas et al., 2010). Office-based buprenorphine treatment for OUD provided in HIV treatment settings has also been associated with decreased opioid use (Fiellin et al., 2011).

In the United States today, the majority of people with HCV have a history of injecting drugs (Norton et al., 2017). A retrospective study of clinical data reported that almost half of people receiving office-based buprenorphine had positive screening tests for HCV antibodies, but only 2 percent had initiated HCV treatment (Carey et al., 2016). Methadone and buprenorphine treatment reduce the risk of HCV infection among injection drug users (Tsui et al., 2014), and people retained in OUD treatment are significantly more likely to initiate HCV treatment (Norton et al., 2017). High rates of successful HCV treatment have been achieved among patients receiving their HCV treatment onsite at OTPs (Butner et al., 2017; Litwin et al., 2009).

RACIAL AND ETHNIC MINORITY POPULATIONS

The demographics of the opioid epidemic in the United States have shifted over the past several years, but according to NSDUH data the prevalence of prescription or illicit opioid misuse has remained lower in racial and ethnic minority groups than among whites (CDC, 2018). Data from the NSDUH suggest that racial minorities are treated less often for their OUD compared with whites (Wu et al., 2016), but existing data regarding how minority populations access medication-based treatment compared with whites are mixed. One study of racial and ethnic differences in the receipt of medication for OUD found that while less than 30 percent of all patients received medication, the odds of receiving it were significantly higher among African American and Hispanic patients who used heroin than among white people who used heroin, which could not be explained by differences in clinical need (Krawczyk et al., 2017a). In contrast, a retrospective cohort study of adolescents and young adults with OUD found that African American and Hispanic patients were significantly less likely than white patients to receive treatment with either buprenorphine or naltrexone within 6 months of diagnosis (Hadland et al., 2017). A retrospective cohort study of urban adults receiving office-based buprenorphine for OUD (2002–2014) found that more than half of all patients were no longer in treatment after 1 year, with significantly worse 1-year treatment retention among people who were African American or Hispanic than among white patients (Weinstein et al., 2017).

African Americans with OUD in the United States have a long history of discrimination, social stigma, and criminalization, as well as limited access to some types of medication-based treatment (Hansen, 2017). For example, in a study of treatment providers in New York City, higher rates of buprenorphine prescription were found in areas with lower concentrations of African American and Latino residents, whereas areas with greater concentrations had higher methadone treatment rates (Hansen et al., 2013). A study of veterans with OUD using Veterans Health Administration treatment services in 2012 confirmed that treatment choices about methadone versus buprenorphine appear to be a function of demographic characteristics rather than of a person's medical, psychiatric, or service-use characteristics—patients who were African American, older, and urban residents were much more likely to receive methadone rather than buprenorphine (Manhapra et al., 2016).

Evidence about OUD among Latino populations in the United States is very limited, and the evidence that is available is mixed. A study of patients receiving methadone maintenance treatment found that Latino patients were significantly more likely to have dropped out of treatment at 6 months (Proctor et al., 2015).

Little is known about the prevalence of OUD treatment among Asian Americans in the United States. However, some research has been carried out among the Hmong population—an ethnic group from Laos—living in Minnesota. Methadone treatment retention after 1 year of treatment was at almost 80 percent among Hmong patients, versus 64 percent among non-Hmong patients; on average, the Hmong patients also required a relatively lower dose of methadone to be stabilized (Bart et al., 2012). Another study of the same population found that Hmong individuals required lower doses of methadone and had significantly lower scores on the psychosocial measures than the non-Hmong participants (Bart, 2018). Native Hawaiians and Pacific Islanders are pooled with Asian Americans in some major data sets—despite being very distinct ethnic groups—so estimates about opioid use and OUD among those populations are particularly limited (Wu et al., 2013).

American Indian and Alaska Native populations are being severely affected by the opioid epidemic, but little evidence is available to understand trends in OUD and medication-based treatment in this group. Limited data indicate that this group has high overdose mortality rates, only slightly lower than whites (Venner et al., 2018). The estimated lifetime prevalence of OUD among Native Americans is very high (Saha et al., 2016). Research and guidance on how to adapt evidence-based programs to be culturally appropriate for these populations is needed (Novins et al., 2011; Venner et al., 2018).

Efforts to expand access to medication-based treatment would benefit greatly from having additional data on treatment for OUD across a diverse range of racial and ethnic groups (Wu et al., 2016). Geographic and demographic variations in medication-based treatment are unknown. The provision of services that are tailored to the unique needs of different ethnic groups is a key factor in effectively treating SUDs among minority populations (Center for Substance Abuse Treatment, 2006). It is important for treatment providers to appreciate how their patients' cultures may inform their particular needs and response to treatment, but it is also important to avoid stereotyping or presuming that all members of a racial or ethnic group are the same (Center for Substance Abuse Treatment, 2006).

LOW SOCIOECONOMIC STATUS AND HOMELESS POPULATIONS

Low socioeconomic status has been associated with greater 12-month and lifetime prevalence rates of prescription OUD (Saha et al., 2016). People of low socioeconomic status with OUD are at a greater risk of becoming homeless (Chatterjee et al., 2018). Whether an individual with OUD is transient, recently displaced, or chronically homeless, it can negatively affect treatment outcomes (Center for Substance Abuse Treatment, 2006).

As many as three-quarters of individuals with SUD who are homeless do not receive any treatment (Magura et al., 2000). Understandably, people who are homeless often struggle to adhere to treatment and tend to drop out early (Lo et al., 2018). However, evidence suggests that office-based buprenorphine treatment can be effectively delivered to people who are homeless, with outcomes comparable to office-based buprenorphine treatment among people who are not homeless (Alford et al., 2007). Proactive case management may help to coordinate social services to provide homeless patients with food, shelter, and transportation to treatment (Center for Substance Abuse Treatment, 2006), as well as providing people who are homeless with overdose education and naloxone prescriptions (Pietrusza et al., 2018).

RURAL AND URBAN POPULATIONS

Research on OUD focused primarily on urban areas during the 1980s and 1990s. However, in the context of the growing opioid crisis, OUD is also epidemic in rural areas, where access to treatment medications is severely limited (Schranz et al., 2018). In fact, the misuse of prescription opioids is now more prevalent in rural than in urban areas (Keyes et al., 2014). More recently, rural communities have seen heroin and fentanyl become even more widely available than prescription opioids on the illicit market (Havens et al., 2018). Heavily rural states have also seen greater increases in opioid-related mortality and injury than non-rural areas (NRHA, 2017).

Factors driving the rural opioid crisis also differ from those driving opioid use in urban areas. Strong social and kinship network connections may facilitate diversion and distribution, while economic stressors may make people more vulnerable to drug use (Keyes et al., 2014). Moreover, compared with urban residents, people living in rural areas face a host of barriers to accessing treatment for OUD. These include provider and community stigma around OUD medications, a lack of public transportation and the need to travel long distances to access care, and severe shortages in the mental and behavioral health workforce (NRHA, 2017). Health care workforce shortages have left between 60 and 80 percent of rural counties without a single psychiatrist and around 40 percent of rural counties without any buprenorphine-waivered physicians (Corso and Townley, 2016; Larson et al., 2016; Leonardson and Gale, 2016; NRHA, 2017; Young et al., 2010). OTPs providing methadone are generally absent from rural areas, and only around 3 percent of primary care providers living in rural areas are waivered to prescribe buprenorphine (Havens et al., 2018). This shortage contributes to the lack of treatment capacity in rural areas (Zur et al., 2018). As a consequence of these bar-

riers, many of the available OUD services are of low quality and do not provide evidence-based treatment for OUD (Havens et al., 2018). Care for the infectious disease sequelae of opioid injection—HIV and HCV—is dependent on a specialized infrastructure that is typically not available in rural areas. These and other barriers to HIV and HCV treatment urgently warrant research (Schranz et al., 2018). One way to address the workforce shortage is to incentivize health care providers to provide OUD treatment in underserved areas (e.g., via loan repayment programs, such as the Health Resources and Services Administration's National Health Service Corps). Another strategy might be to incorporate non-physician providers into rural care settings (NRHA, 2017).

Conclusion 5:
Most people who could benefit from medication-based treatment for opioid use disorder do not receive it, and access is inequitable across subgroups of the population.

Available evidence suggests that medication-based treatment for OUD is highly effective across all subgroups of the population, including adolescents, older persons, pregnant women, individuals with co-occurring disorders (e.g., psychiatric disorders, SUDs, infectious diseases), and all racial, sex and gender, and socioeconomic groups. However, the nature and extent of OUD in these groups appear to vary greatly, as does access to needed medications. To more widely and equitably address the opioid crisis, additional study will be required of the significance and causes of these differences as well as of the potential need for specific medication-based treatment guidelines for subpopulations.

REFERENCES

Adelson, M., S. Linzy, and E. Peles. 2018. Characteristics and outcome of male and female methadone maintenance patients: MMT in Tel Aviv and Las Vegas. *Substance Use & Misuse* 53(2):230–238.

Alford, D. P., C. T. LaBelle, J. M. Richardson, J. J. O'Connell, C. A. Hohl, D. M. Cheng, and J. H. Samet. 2007. Treating homeless opioid dependent patients with buprenorphine in an office-based setting. *Journal of General Internal Medicine* 22(2):171–176.

Back, S. E., R. L. Payne, A. N. Simpson, and K. T. Brady. 2010. Gender and prescription opioids: Findings from the National Survey on Drug Use and Health. *Addictive Behaviors* 35(11):1001–1007.

Back, S. E., K. M. Lawson, L. M. Singleton, and K. T. Brady. 2011. Characteristics and correlates of men and women with prescription opioid dependence. *Addictive Behaviors* 36(8):829–834.

Barocas, J. D., L. F. White, J. Wang, A. Y. Walley, M. R. LaRochelle, D. Bernson, T. Land, J. R. Morgan, J. H. Samet, and B. P. Linas. 2018. Estimated prevalence of opioid use disorder in Massachusetts, 2011–2015: A capture–recapture analysis. *American Journal of Public Health* 108(12):1675–1681.

Bart, G. 2018. Ethnic differences in psychosocial factors in methadone maintenance: Hmong versus non-Hmong. *Journal of Ethnicity in Substance Abuse* 17(2):108–122.

Bart, G., Q. Wang, J. S. Hodges, C. Nolan, and G. Carlson. 2012. Superior methadone treatment outcome in Hmong compared with non-Hmong patients. *Journal of Substance Abuse Treatment* 43(3):269–275.

Bartley, E. J., and R. B. Fillingim. 2013. Sex differences in pain: A brief review of clinical and experimental findings. *British Journal of Anaesthesiology* 111(1):52–58.

Bawor, M., B. B. Dennis, M. Varenbut, J. Daiter, D. C. Marsh, C. Plater, A. Worster, M. Steiner, R. Anglin, G. Pare, D. Desai, L. Thabane, and Z. Samaan. 2015. Sex differences in substance use, health, and social functioning among opioid users receiving methadone treatment: A multicenter cohort study. *Biology of Sex Differences* 6:21.

Berg, K. M., A. Litwin, X. Li, M. Heo, and J. H. Arnsten. 2011. Directly observed antiretroviral therapy improves adherence and viral load in drug users attending methadone maintenance clinics: A randomized controlled trial. *Drug and Alcohol Dependence* 113(2–3):192–199.

Butner, J. L., N. Gupta, C. Fabian, S. Henry, J. M. Shi, and J. M. Tetrault. 2017. Onsite treatment of HCV infection with direct acting antivirals within an opioid treatment program. *Journal of Substance Abuse Treatment* 75:49–53.

Carey, K. J., W. Huang, B. P. Linas, and J. I. Tsui. 2016. Hepatitis C virus testing and treatment among persons receiving buprenorphine in an office-based program for opioid use disorders. *Journal of Substance Abuse Treatment* 66:54–59.

Casey, B. J., R. M. Jones, and T. A. Hare. 2008. The adolescent brain. *Annals of the New York Academy of Sciences* 1124:111–126.

CDC (U.S. Centers for Disease Control and Prevention). 2018. *2018 annual surveillance report of drug-related risks and outcomes*. Atlanta, GA: CDC National Center for Injury Prevention and Control.

Center for Substance Abuse Treatment. 2006. Chapter 9. Adapting intensive outpatient treatment for specific populations. In *Substance abuse: Clinical issues in intensive outpatient treatment*. Treatment improvement protocol (TIP) series. Rockville, MD: Substance Abuse and Mental Health Services Administration.

Center for Substance Abuse Treatment. 2012. *Managing chronic pain in adults with or in recovery from substance use disorders*, *Treatment improvement protocol (TIP) series, no. 54*. Rockville, MD: Substance Abuse and Mental Health Services Administration.

Chang, D. C., J. Klimas, E. Wood, and N. Fairbairn. 2018. Medication-assisted treatment for youth with opioid use disorder: Current dilemmas and remaining questions. *American Journal of Drug and Alcohol Abuse* 44(2):143–146.

Charney, D. A., A. M. Paraherakis, and K. J. Gill. 2001. Integrated treatment of comorbid depression and substance use disorders. *Journal of Clinical Psychiatry* 62(9):672–677.

Chatterjee, A., E. J. Yu, and L. Tishberg. 2018. Exploring opioid use disorder, its impact, and treatment among individuals experiencing homelessness as part of a family. *Drug and Alcohol Dependence* 188:161–168.

Cicero, T. J., G. Wong, Y. Tian, M. Lynskey, A. Todorov, and K. Isenberg. 2009. Co-morbidity and utilization of medical services by pain patients receiving opioid medications: Data from an insurance claims database. *Pain* 144(1–2):20–27.

Cicero, T. J., M. S. Ellis, H. L. Surratt, and S. P. Kurtz. 2014. The changing face of heroin use in the United States: A retrospective analysis of the past 50 years. *JAMA Psychiatry* 71(7):821–826.

Clay, S. W. 2010. Treatment of addiction in the elderly. *Aging Health* 6(2):177–189.

Committee on Substance Use and Prevention. 2016. Medication-assisted treatment of adolescents with opioid use disorders. *Pediatrics* 138(3):e20161893.

Connery, H. S. 2015. Medication-assisted treatment of opioid use disorder: Review of the evidence and future directions. *Harvard Review of Psychiatry* 23(2):63–75.

Corso, C., and C. Townley. 2016. *Intervention, treatment, and prevention strategies to address opioid use disorders in rural areas*. National Academy for State Health Policy. https://nashp.org/wp-content/uploads/2016/09/Rural-Opioid-Primer.pdf (accessed February 11, 2019).

Cunningham, C. O., A. Giovanniello, H. V. Kunins, R. J. Roose, A. D. Fox, and N. L. Sohler. 2013. Buprenorphine treatment outcomes among opioid-dependent cocaine users and non-users. *American Journal on Addiction* 22(4):352–357.

Daitch, D., J. Daitch, D. Novinson, M. Frey, C. Mitnick, and J. Pergolizzi. 2014. Conversion from high-dose full-opioid agonists to sublingual buprenorphine reduces pain scores and improves quality of life for chronic pain patients. *Pain Medicine* 15(12):2087–2094.

David, S., T. Lancaster, L. F. Stead, and A. E. Evins. 2006. Opioid antagonists for smoking cessation. *Cochrane Database of Systematic Reviews* 2006(4):CD003086.

Delorme, J., C. Chenaf, C. Bertin, M. Riquelme, A. Eschalier, D. Ardid, and N. Authier. 2018. Chronic pain opioid-maintained patients receive less analgesic opioid prescriptions. *Frontiers in Psychiatry* 9:335.

Dennis, B. B., M. Bawor, L. Naji, C. K. Chan, J. Varenbut, J. Paul, M. Varenbut, J. Daiter, C. Plater, G. Pare, D. C. Marsh, A. Worster, D. Desai, L. Thabane, and Z. Samaan. 2015. Impact of chronic pain on treatment prognosis for patients with opioid use disorder: A systematic review and meta-analysis. *Substance Abuse: Research and Treatment* 9:59–80.

Dhingra, L., C. Masson, D. C. Perlman, R. M. Seewald, J. Katz, C. McKnight, P. Homel, E. Wald, A. E. Jordan, C. Young, and R. K. Portenoy. 2012. Epidemiology of pain among outpatients in methadone maintenance treatment programs. *Drug and Alcohol Dependence* 128(1–2):161–165.

Doyle, H. H., and A. Z. Murphy. 2018. Sex-dependent influences of morphine and its metabolites on pain sensitivity in the rat. *Physiology & Behavior* 187:32–41.

Drake, R. E., and K. T. Mueser. 2000. Psychosocial approaches to dual diagnosis. *Schizophrenia Bulletin* 26(1):105–118.

Dreifuss, J. A., M. L. Griffin, K. Frost, G. M. Fitzmaurice, J. S. Potter, D. A. Fiellin, J. Selzer, M. Hatch-Maillette, S. C. Sonne, and R. D. Weiss. 2013. Patient characteristics associated with buprenorphine/naloxone treatment outcome for prescription opioid dependence: Results from a multisite study. *Drug and Alcohol Dependence* 131(1–2):112–118.

Duncan, D. T., S. Zweig, H. R. Hambrick, and J. J. Palamar. 2019. Sexual orientation disparities in prescription opioid misuse among U.S. adults. *American Journal of Preventive Medicine* 56(1):17–26.

Elliott, J. C., M. J. Picker, A. J. Sparrow, and D. T. Lysle. 2006. Dissociation between sex differences in the immunological, behavioral, and physiological effects of kappa- and delta-opioids in Fischer rats. *Psychopharmacology (Berl)* 185(1):66–75.

Evans, E., A. Kelleghan, L. Li, J. Min, D. Huang, D. Urada, Y. I. Hser, and B. Nosyk. 2015. Gender differences in mortality among treated opioid dependent patients. *Drug and Alcohol Dependence* 155:228–235.

Fanucchi, L., S. A. Springer, and P. T. Korthuis. 2019. Medications for treatment of opioid use disorder among persons living with HIV. *Current HIV/AIDS Reports* 2019:1–6.

FDA (U.S. Food and Drug Administration). 2017. Statement from FDA commissioner Scott Gottlieb, M.D., on the agency's continued efforts to promote the sage adoption of medication-assisted treatment for opioid addiction. *FDA News and Events,* September 20. https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm576752.htm (accessed February 11, 2019).

Feder, K. A., N. Krawczyk, and B. Saloner. 2017. Medication-assisted treatment for adolescents in specialty treatment for opioid use disorder. *Journal of Adolescent Health* 60(6):747–750.

Fiellin, D. A., L. Weiss, M. Botsko, J. E. Egan, F. L. Altice, L. B. Bazerman, A. Chaudhry, C. O. Cunningham, M. N. Gourevitch, P. J. Lum, L. E. Sullivan, R. S. Schottenfeld, P. G. O'Connor, and B. Collaborative. 2011. Drug treatment outcomes among HIV-infected opioid-dependent patients receiving buprenorphine/naloxone. *Journal of Acquired Immune Deficiency Syndromes (1999)* 56(Suppl 1):S33–S38.

Fillingim, R. B., C. D. King, M. C. Ribeiro-Dasilva, B. Rahim-Williams, and J. L. Riley. 2009. Sex, gender, and pain: A review of recent clinical and experimental findings. *The Journal of Pain* 10(5):447–485.

Flynn, P. M., S. G. Craddock, J. W. Luckey, R. L. Hubbard, and G. H. Dunteman. 1996. Comorbidity of antisocial personality and mood disorders among psychoactive substance-dependent treatment clients. *Journal of Personality Disorders* 10(1):56–67.

Fox, A. D., N. L. Sohler, J. L. Starrels, Y. Ning, A. Giovanniello, and C. O. Cunningham. 2012. Pain is not associated with worse office-based buprenorphine treatment outcomes. *Substance Abuse* 33(4):361–365.

Frimpong, J. A., K. Shiu, T. D'Aunno, H. Pollack, and P. Friedmann. 2017. Gender differences in methadone dose patterns and length of treatment in outpatient methadone maintenance treatment programs. *Drug and Alcohol Dependence* 171:e66.

Gardner, E. M., M. P. McLees, J. F. Steiner, C. del Rio, and W. J. Burman. 2011. The spectrum of engagement in HIV care and its relevance to test-and-treat strategies for prevention of HIV infection. *Clinical Infectious Diseases* 52(6):793–800.

Girouard, M. P., H. Goldhammer, and A. S. Keuroghlian. 2019. Understanding and treating opioid use disorders in lesbian, gay, bisexual, transgender, and queer populations. *Substance Abuse* 2019:1–5.

Gourevitch, M. N., and G. H. Friedland. 2000. Interactions between methadone and medications used to treat HIV infection: A review. *Mount Sinai Journal of Medicine* 67(5–6):429–436.

Gowing, L., M. F. Farrell, R. Bornemann, L. E. Sullivan, and R. Ali. 2011. Oral substitution treatment of injecting opioid users for prevention of HIV infection. *Cochrane Database of Systematic Reviews* 2011(8):CD004145.

Gowing, L., R. Ali, J. M. White, and D. Mbewe. 2017. Buprenorphine for managing opioid withdrawal. *Cochrane Database of Systematic Reviews* 2017(2):CD002025.

Grella, C. E., M. P. Karno, U. S. Warda, N. Niv, and A. A. Moore. 2009. Gender and comorbidity among individuals with opioid use disorders in the NESARC study. *Addictive Behaviors* 34(6–7):498–504.

Griffith, J. D., G. A. Rowan-Szal, R. R. Roark, and D. D. Simpson. 2000. Contingency management in outpatient methadone treatment: A meta-analysis. *Drug and Alcohol Dependence* 58(1–2):55–66.

Hadland, S. E., J. W. Frank Wharam, M. A. Schuster, F. Zhang, J. H. Samet, and M. R. Larochelle. 2017. Trends in receipt of buprenorphine and naltrexone for opioid use disorder among adolescents and young adults, 2001–2014. *JAMA Pediatrics* 171(8):747–755.

Hadland, S. E., S. M. Bagley, J. Rodean, M. Silverstein, S. Levy, M. R. Larochelle, J. H. Samet, and B. T. Zima. 2018a. Receipt of timely addiction treatment and association of early medication treatment with retention in care among youths with opioid use disorder. *JAMA Pediatrics* 172(11):1029–1037.

Hadland, S. E., T. W. Park, and S. M. Bagley. 2018b. Stigma associated with medication treatment for young adults with opioid use disorder: A case series. *Addiction Science & Clinical Practice* 13(1):15.

Haight, S. C., J. Y. Ko, V. T. Tong, M. K. Bohm, and W. M. Callaghan. 2018. Opioid use disorder documented at delivery hospitalization—United States, 1999–2014. *Morbidity and Mortality Weekly Report* 67(31):845–849.

Hall, M. T., J. Wilfong, R. A. Huebner, L. Posze, and T. Willauer. 2016. Medication-assisted treatment improves child permanency outcomes for opioid-using families in the child welfare system. *Journal of Substance Abuse Treatment* 71:63–67.

Hansen, H. 2017. Sociocultural factors impacting access to MAT and care delivery: New qualitative data from buprenorphine prescribers in OTPS. *American Journal on Addictions* 26(3):236.

Hansen, H. B., C. E. Siegel, B. G. Case, D. N. Bertollo, D. DiRocco, and M. Galanter. 2013. Variation in use of buprenorphine and methadone treatment by racial, ethnic, and income characteristics of residential social areas in New York City. *Journal of Behavioral Health Services & Research* 40(3):367–377.

Havens, J. R., S. L. Walsh, P. T. Korthuis, and D. A. Fiellin. 2018. Implementing treatment of opioid-use disorder in rural settings: A focus on HIV and hepatitis C prevention and treatment. *Current HIV/AIDS Reports* 15(4):315–323.

Hernandez-Avila, C. A., B. J. Rounsaville, and H. R. Kranzler. 2004. Opioid-, cannabis- and alcohol-dependent women show more rapid progression to substance abuse treatment. *Drug and Alcohol Dependence* 74(3):265–272.

Jones, E. S., and D. A. Fiellin. 2007. Women and opioid dependence treatment: Office-based versus opioid treatment program-based care? *Substance Abuse* 28(2):3–8.

Jones, H. E., K. Kaltenbach, S. H. Heil, S. M. Stine, M. G. Coyle, A. M. Arria, K. E. O'Grady, P. Selby, P. R. Martin, and G. Fischer. 2010. Neonatal abstinence syndrome after methadone or buprenorphine exposure. *New England Journal of Medicine* 363(24):2320–2331.

Kaltenbach, K., and L. P. Finnegan. 1984. Developmental outcome of children born to methadone maintained women: A review of longitudinal studies. *Neurobehavioral Toxicology and Teratology* 6(4):271–275.

Keyes, K. M., M. Cerda, J. E. Brady, J. R. Havens, and S. Galea. 2014. Understanding the rural-urban differences in nonmedical prescription opioid use and abuse in the United States. *American Journal of Public Health* 104(2):e52–e59.

Klaman, S. L., K. Isaacs, A. Leopold, J. Perpich, S. Hayashi, J. Vender, M. Campopiano, and H. E. Jones. 2017. Treating women who are pregnant and parenting for opioid use disorder and the concurrent care of their infants and children: Literature review to support national guidance. *Journal of Addiction Medicine* 11(3):178–190.

Klimas, J., E. Wood, E. Nosova, M. J. Milloy, T. Kerr, and K. Hayashi. 2018. Prevalence of heavy alcohol use among people receiving methadone following change to methadose. *Substance Use and Misuse* 53(2):270–275.

Knudsen, H. K., A. J. Abraham, and P. M. Roman. 2011. Adoption and implementation of medications in addiction treatment programs. *Journal of Addiction Medicine* 5(1):21–27.

Kosten, T. R., C. M. Morgan, J. Falcione, and R. S. Schottenfeld. 1992. Pharmacotherapy for cocaine-abusing methadone-maintained patients using amantadine or desipramine. *Archives of General Psychiatry* 49(11):894–898.

Kotelchuck, M., E. R. Cheng, C. Belanoff, H. J. Cabral, H. Babakhanlou-Chase, T. M. Derrington, H. Diop, S. R. Evans, and J. Bernstein. 2017. The prevalence and impact of substance use disorder and treatment on maternal obstetric experiences and birth outcomes among singleton deliveries in Massachusetts. *Maternal and Child Health Journal* 21(4):893–902.

Krawczyk, N., K. A. Feder, M. I. Fingerhood, and B. Saloner. 2017a. Racial and ethnic differences in opioid agonist treatment for opioid use disorder in a U.S. national sample. *Drug and Alcohol Dependence* 178:512–518.

Krawczyk, N., K. A. Feder, B. Saloner, R. M. Crum, M. Kealhofer, and R. Mojtabai. 2017b. The association of psychiatric comorbidity with treatment completion among clients admitted to substance use treatment programs in a U.S. national sample. *Drug and Alcohol Dependence* 175:157–163.

Larney, S., A. S. B. Bohnert, D. Ganoczy, M. A. Ilgen, M. Hickman, F. C. Blow, and L. Degenhardt. 2015. Mortality among older adults with opioid use disorders in the Veterans Health Administration, 2000–2011. *Drug and Alcohol Dependence* 147:32–37.

Larson, E., D. Patterson, L. Garberson, and C. Andrilla. 2016. *Supply and distribution of the behavioral health workforce in rural America*. Seattle, WA: Washington, Wyoming, Alaska, Montana, Idaho Rural Health Center, University of Washington.

Leonardson, J., and J. Gale. 2016. *Distribution of substance abuse treatment facilities across the rural–urban continuum*. Maine Rural Health Research Center working paper no. 35. https://muskie.usm.maine.edu/Publications/rural/wp35b.pdf (accessed February 11, 2019).

Levine, A. R., L. H. Lundahl, D. M. Ledgerwood, M. Lisieski, G. L. Rhodes, and M. K. Greenwald. 2015. Gender-specific predictors of retention and opioid abstinence during methadone maintenance treatment. *Journal of Substance Abuse Treatment* 54:37–43.

Litwin, A. H., K. A. Harris, S. Nahvi, P. J. Zamor, I. J. Soloway, P. L. Tenore, D. Kaswan, M. N. Gourevitch, and J. H. Arnsten. 2009. Successful treatment of chronic hepatitis C with peglyated interferon in combination with ribavirin in a methadone maintenance treatment program. *Journal of Substance Abuse Treatment* 37(1):32–40.

Litz, M., and D. Leslie. 2017. The impact of mental health comorbidities on adherence to buprenorphine: A claims based analysis. *American Journal on Addictions* 26(8):859–863.

Lo, A., T. Kerr, K. Hayashi, M. J. Milloy, E. Nosova, Y. Liu, and N. Fairbairn. 2018. Factors associated with methadone maintenance therapy discontinuation among people who inject drugs. *Journal of Substance Abuse Treatment* 94:41–46.

Low, A. J., G. Mburu, N. J. Welton, M. T. May, C. F. Davies, C. French, K. M. Turner, K. J. Looker, H. Christensen, S. McLean, T. Rhodes, L. Platt, M. Hickman, A. Guise, and P. Vickerman. 2016. Impact of opioid substitution therapy on antiretroviral therapy outcomes: A systematic review and meta-analysis. *Clinical Infectious Diseases* 63(8):1094–1104.

Loyd, D. R., and A. Z. Murphy. 2009. The role of the periaqueductal gray in the modulation of pain in males and females: Are the anatomy and physiology really that different? *Neural Plasticity* 2009:462879.

Lucas, G. M., A. Chaudry, J. Hsu, T. Woodson, B. Lau, Y. Olsen, J. C. Keruly, D. A. Fiellin, R. Finkelstein, P. Barditch-Crovo, K. Cook, and R. D. Moore. 2010. Clinic-based treatment of opioid-dependent HIV infected patients versus referral to an opioid treatment program: A randomized trial. *Annals of Medicine* 152(11):704–711.

Lugoboni, F., F. R. Levin, M. C. Pieri, M. Manfredini, L. Zamboni, L. Somaini, G. Gerra, and GICS. 2017. Co-occurring attention deficit hyperactivity disorder symptoms in adults affected by heroin dependence: Patients characteristics and treatment needs. *Psychiatry Research* 250:210–216.

Lund, I. O., G. Fischer, G. K. Welle-Strand, K. E. O'Grady, K. Debelak, W. R. Morrone, and H. E. Jones. 2013. A comparison of buprenorphine + naloxone to buprenorphine and methadone in the treatment of opioid dependence during pregnancy: Maternal and neonatal outcomes. *Substance Abuse: Research and Treatment* 7:61–74.

Magura, S., P. C. Nwakeze, A. Rosenblum, and H. Joseph. 2000. Substance misuse and related infectious diseases in a soup kitchen population. *Substance Use and Misuse* 35(4):551–583.

Manhapra, A., L. Quinones, and R. Rosenheck. 2016. Characteristics of veterans receiving buprenorphine vs. methadone for opioid use disorder nationally in the Veterans Health Administration. *Drug and Alcohol Dependence* 160:82–89.

Mannelli, P., L. T. Wu, K. S. Peindl, and D. A. Gorelick. 2013. Smoking and opioid detoxification: Behavioral changes and response to treatment. *Nicotine and Tobacco Research* 15(10):1705–1713.

Manubay, J., J. Davidson, S. Vosburg, J. Jones, S. Comer, and M. Sullivan. 2015. Sex differences among opioid-abusing chronic pain patients in a clinical trial. *Journal of Addiction Medicine* 9(1):46–52.

Marsch, L. A., M. A. C. Stephens, T. Mudric, E. C. Strain, G. E. Bigelow, and R. E. Johnson. 2005. Predictors of outcome in LAAM, buprenorphine, and methadone treatment for opioid dependence. *Experimental and Clinical Psychopharmacology* 13(4):293–302.

Marsh, J. C., T. A. D'Aunno, and B. D. Smith. 2000. Increasing access and providing social services to improve drug abuse treatment for women with children. *Addiction* 95(8):1237–1247.

Matson, S. C., G. Hobson, M. Abdel-Rasoul, and A. E. Bonny. 2014. A retrospective study of retention of opioid-dependent adolescents and young adults in an outpatient buprenorphine/naloxone clinic. *Journal of Addiction Medicine* 8(3):176–182.

Mazure, C. M., and D. A. Fiellin. 2018. Women and opioids: Something different is happening here. *Lancet* 392(10141):9–11.

Mbaba, M., S. E. Brown, A. Wooditch, M. Kiss, A. Murphy, S. Kumari, F. Taxman, F. Altice, W. B. Lawson, and S. A. Springer. 2018. Prevalence, diagnosis, and treatment rates of mood disorders among opioid users under criminal justice supervision. *Substance Use & Misuse* 53(9):1519–1528.

McCance-Katz, E. F., D. E. Moody, G. D. Morse, Q. Ma, R. DiFrancesco, G. Friedland, P. Pade, and P. M. Rainey. 2007. Interaction between buprenorphine and atazanavir or atazanavir/ritonavir. *Drug & Alcohol Dependence* 91(2–3):269–278.

McHugh, R. K., E. E. DeVito, D. Dodd, K. M. Carroll, J. S. Potter, S. F. Greenfield, H. S. Connery, and R. D. Weiss. 2013. Gender differences in a clinical trial for prescription opioid dependence. *Journal of Substance Abuse Treatment* 45(1):38–43.

Messina, N., S. Calhoun, and J. Braithwaite. 2014. Trauma-informed treatment decreases posttraumatic stress disorder among women offenders. *Journal of Trauma & Dissociation* 15(1):6–23.

Metz, V. E., Q. L. Brown, S. S. Martins, and J. J. Palamar. 2018. Characteristics of drug use among pregnant women in the United States: Opioid and non-opioid illegal drug use. *Drug and Alcohol Dependence* 183:261–266.

Minozzi, S., L. Amato, C. Bellisario, M. Ferri, and M. Davoli. 2013. Maintenance agonist treatments for opiate-dependent pregnant women. *Cochrane Database of Systematic Reviews* 2013(12):CD006318.

Nahvi, S., O. Blackstock, N. L. Sohler, D. Thompson, and C. O. Cunningham. 2014a. Smoking cessation treatment among office-based buprenorphine treatment patients. *Journal of Substance Abuse Treatment* 47(2):175–179.

Nahvi, S. Y. Ning, K. S. Segal, K. P. Richter, and J. H. Arnsten. 2014b. Varenicline efficacy and safety among methadone maintained smokers: A randomized placebo-controlled trial. *Addiction* 109(9):1554–1563.

NASEM (National Academies of Sciences, Engineering, and Medicine). 2018. *Integrating responses at the intersection of opioid use disorder and infectious disease epidemics: Proceedings of a workshop*. Washington, DC: The National Academies Press.

Norton, B. L., A. Beitin, M. Glenn, J. DeLuca, A. H. Litwin, and C. O. Cunningham. 2017. Retention in buprenorphine treatment is associated with improved HCV care outcomes. *Journal of Substance Abuse Treatment* 75:38–42.

Novins, D. K., G. A. Aarons, S. G. Conti, D. Dahlke, R. Daw, A. Fickenscher, C. Fleming, C. Love, K. Masis, P. Spicer, and the Centers for American Indian and Alaska Native Health's Substance Abuse Treatment Advisory Board. 2011. Use of the evidence base in substance abuse treatment programs for American Indians and Alaska Natives: Pursuing quality in the crucible of practice and policy. *Implementation Science* 6(1):63.

NRHA (National Rural Health Association). 2017. *Policy brief: Treating the rural opioid epidemic*. https://www.ruralhealthweb.org/NRHA/media/Emerge_NRHA/Advocacy/Policy%20documents/Treating-the-Rural-Opioid-Epidemic_Feb-2017_NRHA-Policy-Paper.pdf (accessed February 11, 2019).

Ouimette, P. C., R. Kimerling, J. Shaw, and R. H. Moos. 2000. Physical and sexual abuse among women and men with substance use disorders. *Alcoholism Treatment Quarterly* 18(3):7–17.

Pade, P. A., K. E. Cardon, R. M. Hoffman, and C. M. Geppert. 2012. Prescription opioid abuse, chronic pain, and primary care: A co-occurring disorders clinic in the chronic disease model. *Journal of Substance Abuse Treatment* 43(4):446–450.

Peckham, E. M., and J. R. Traynor. 2006. Comparison of the antinociceptive response to morphine and morphine-like compounds in male and female Sprague–Dawley rats. *Journal of Pharmacology and Experimental Therapeutics* 316(3):1195–1201.

Perlman, D. C., and A. E. Jordan. 2018. The syndemic of opioid misuse, overdose, HCV, and HIV: Structural-level causes and interventions. *Current HIV/AIDS Reports* 15(2):96–112.

Pietrusza, L. M., K. R. Puskar, D. Ren, and A. M. Mitchell. 2018. Evaluation of an opiate overdose educational intervention and naloxone prescribing program in homeless adults who use opiates. *Journal of Addictions Nursing* 29(3):188–195.

Priester, M. A., T. Browne, A. Iachini, S. Clone, D. DeHart, and K. D. Seay. 2016. Treatment access barriers and disparities among individuals with co-occurring mental health and substance use disorders: An integrative literature review. *Journal of Substance Abuse Treatment* 61:47–59.

Proctor, S. L., A. L. Copeland, A. M. Kopak, N. G. Hoffmann, P. L. Herschman, and N. Polukhina. 2015. Predictors of patient retention in methadone maintenance treatment. *Psychology of Addictive Behaviors* 29(4):906–917.

Rich, K. M., J. Bia, F. L. Altice, and J. Feinberg. 2018. Integrated models of care for individuals with opioid use disorder: How do we prevent HIV and HCV? *Current HIV/AIDS Reports* 15(3):266–275.

Robertson, A. G., M. M. Easter, H. J. Lin, L. K. Frisman, J. W. Swanson, and M. S. Swartz. 2018. Associations between pharmacotherapy for opioid dependence and clinical and criminal justice outcomes among adults with co-occurring serious mental illness. *Journal of Substance Abuse Treatment* 86:17–25.

Rosenblum, A., H. Joseph, C. Fong, S. Kipnis, C. Cleland, and R. K. Portenoy. 2003. Prevalence and characteristics of chronic pain among chemically dependent patients in methadone maintenance and residential treatment facilities. *JAMA* 289(18):2370–2378.

Rosic, T., L. Naji, M. Bawor, B. B. Dennis, C. Plater, D. C. Marsh, L. Thabane, and Z. Samaan. 2017. The impact of comorbid psychiatric disorders on methadone maintenance treatment in opioid use disorder: A prospective cohort study. *Neuropsychiatric Disease and Treatment* 13:1399–1408.

Saha, T. D., B. T. Kerridge, R. B. Goldstein, S. P. Chou, H. Zhang, J. Jung, R. P. Pickering, W. J. Ruan, S. M. Smith, B. Huang, D. S. Hasin, and B. F. Grant. 2016. Nonmedical prescription opioid use and DSM-5 nonmedical prescription opioid use disorder in the United States. *Journal of Clinical Psychiatry* 77(6):772–780.

SAMHSA (Substance Abuse and Mental Health Services Administration). 2017. *Opioid use in the older adult population*. https://www.samhsa.gov/capt/sites/default/files/resources/resources-opiod-use-older-adult-pop.pdf (accessed February 9, 2019).

SAMHSA. 2018. *Key substance use and mental health indicators in the United States: Results from the 2017 National Survey on Drug Use and Health*. https://www.samhsa.gov/data/sites/default/files/cbhsq-reports/NSDUHFFR2017/NSDUHFFR2017.pdf (accessed December 12, 2018).

Santoro, G. C., J. Carrion, and S. L. Dewey. 2017a. Imaging sex differences in regional brain metabolism during acute opioid withdrawal. *Journal of Alcoholism and Drug Dependence* 5(2):pii:262.

Santoro, G. C., J. Carrion, K. Patel, C. Vilchez, J. Veith, J. D. Brodie, and S. L. Dewey. 2017b. Sex differences in regional brain glucose metabolism following opioid withdrawal and replacement. *Neuropsychopharmacology* 42(9):1841–1849.

Schiff, D. M., T. Nielsen, M. Terplan, M. Hood, D. Bernson, H. Diop, M. Bharel, T. E. Wilens, M. LaRochelle, A. Y. Walley, and T. Land. 2018. Fatal and nonfatal overdose among pregnant and postpartum women in Massachusetts. *Obstetrics and Gynecology* 132(2):466–474.

Schranz, A. J., J. Barrett, C. B. Hurt, C. Malvestutto, and W. C. Miller. 2018. Challenges facing a rural opioid epidemic: Treatment and prevention of HIV and hepatitis C. *Current HIV/AIDS Reports* 15(3):245–254.

Schuman-Olivier, Z., R. D. Weiss, B. B. Hoeppner, J. Borodovsky, and M. J. Albanese. 2014. Emerging adult age status predicts poor buprenorphine treatment retention. *Journal of Substance Abuse Treatment* 47(3):202–212.

Serdarevic, M., C. W. Striley, and L. B. Cottler. 2017. Sex differences in prescription opioid use. *Current Opinion in Psychiatry* 30(4):238–246.

Short, V. L., D. J. Hand, L. MacAfee, D. J. Abatemarco, and M. Terplan. 2018. Trends and disparities in receipt of pharmacotherapy among pregnant women in publically funded treatment programs for opioid use disorder in the United States. *Journal of Substance Abuse Treatment* 89:67–74.

Socias, M. E., N. Volkow, and E. Wood. 2016. Adopting the "Cascade of Care" framework: An opportunity to close the implementation gap in addiction care? *Addiction* 111(12):2079–2081.

Stimmel, B., and K. Adamsons. 1976. Narcotic dependency in pregnancy. Methadone maintenance compared to use of street drugs. *JAMA* 235(11):1121–1124.

Strain, E. C. 2002. Assessment and treatment of comorbid psychiatric disorders in opioid-dependent patients. *Clinical Journal of Pain* 18(4):S14–S27.

Sullivan, L. E., B. A. Moore, P. G. O'Connor, D. T. Barry, M. C. Chawarski, R. S. Schottenfeld, and D. A. Fiellin. 2010. The association between cocaine use and treatment outcomes in patients receiving office-based buprenorphine/naloxone for the treatment of opioid dependence. *American Journal of Addiction* 19(1):53–58.

Terplan, M., N. Longinaker, and L. Appel. 2015. Women-centered drug treatment services and need in the United States, 2002–2009. *American Journal of Public Health* 105(11):e50–e54.

Torchalla, I., I. A. Linden, V. Strehlau, E. K. Neilson, and M. Krausz. 2015. "Like a lots happened with my whole childhood": Violence, trauma, and addiction in pregnant and postpartum women from Vancouver's Downtown Eastside. *Harm Reduction Journal* 11:34.

Tsui, J. I., J. L. Evans, P. J. Lum, J. A. Hahn, and K. Page. 2014. Association of opioid agonist therapy with lower incidence of hepatitis C virus infection in young adult injection drug users. *JAMA Internal Medicine* 174(12):1974–1981.

Venner, K. L., D. M. Donovan, A. N. C. Campbell, D. C. Wendt, T. Rieckmann, S. M. Radin, S. L. Momper, and C. L. Rosa. 2018. Future directions for medication assisted treatment for opioid use disorder with American Indian/Alaska Natives. *Addictive Behaviors* 86:111–117.

Wang, P. W., H. C. Lin, Y. C. Yang, C. Y. Hsu, K. S. Chung, H. C. Wu, and C. F. Yen. 2017. Gender and age effects on the trajectory of depression in opioid users during methadone maintenance treatment. *Frontiers in Psychiatry* 8:288.

Watkins, K. E., A. Burnam, F. Y. Kung, and S. Paddock. 2001. A national survey of care for persons with co-occurring mental and substance use disorders. *Psychiatric Services* 52(8):1062–1068.

Weinberg, N. Z., E. Rahdert, J. D. Colliver, and M. D. Glantz. 1998. Adolescent substance abuse: A review of the past 10 years. *Journal of the American Academy of Child and Adolescent Psychiatry* 37(3):252–261.

Weinstein, Z. M., H. W. Kim, D. M. Cheng, E. Quinn, D. Hui, C. T. Labelle, M. L. Drainoni, S. S. Bachman, and J. H. Samet. 2017. Long-term retention in office-based opioid treatment with buprenorphine. *Journal of Substance Abuse Treatment* 74:65–70.

Whitesell, M., A. Bachand, J. Peel, and M. Brown. 2013. Familial, social, and individual factors contributing to risk for adolescent substance use. *Journal of Addiction* 2013:579310.

Williams, A. R., E. V. Nunes, and M. Olfson. 2017. *To battle the opioid overdose epidemic, deploy the "Cascade of Care" model*. Health Affairs blog. https://www.healthaffairs.org/do/10.1377/hblog20170313.059163/full (accessed February 11, 2019).

Williams, A. R., E. V. Nunes, A. Bisaga, H. A. Pincus, K. A. Johnson, A. N. Campbell, R. H. Remien, S. Crystal, P. D. Friedmann, F. R. Levin, and M. Olfson. 2018. Developing an opioid use disorder treatment cascade: A review of quality measures. *Journal of Substance Abuse Treatment* 91:57–68.

Woody, G. E., S. A. Poole, G. Subramaniam, K. Dugosh, M. Bogenschutz, P. Abbott, A. Patkar, M. Publicker, K. McCain, J. S. Potter, R. Forman, V. Vetter, L. McNicholas, J. Blaine, K. G. Lynch, and P. Fudala. 2008. Extended vs. short-term buprenorphine–naloxone for treatment of opioid-addicted youth: A randomized trial. *JAMA* 300(17):2003–2011. [Erratum appears in *JAMA*, February 25, 2009; 301(8):830.] [Erratum appears in *JAMA*, April 10, 2013; 309(14):1461.]

Woody, G. E., D. Bruce, P. T. Korthuis, S. Chhatre, S. Poole, M. Hillhouse, P. Jacobs, J. Sorensen, A. J. Saxon, D. Metzger, and W. Ling. 2014. HIV risk reduction with buprenorphine-naloxone or methadone: Findings from a randomized trial. *Journal of Acquired Immune Deficiency Syndromes* 66(3):288–293.

Worley, M. J., K. G. Heinzerling, S. Shoptaw, and W. Ling. 2017. Volatility and change in chronic pain severity predict outcomes of treatment for prescription opioid addiction. *Addiction* 112(7):1202–1209.

Wu, L.-T., D. G. Blazer, M. S. Swartz, B. Burchett, K. T. Brady, and N. A. Workgroup. 2013. Illicit and nonmedical drug use among Asian Americans, native Hawaiians/Pacific Islanders, and mixed-race individuals. *Drug and Alcohol Dependence* 133(2):360–367.

Wu, L.-T., H. Zhu, and M. S. Swartz. 2016. Treatment utilization among persons with opioid use disorder in the United States. *Drug and Alcohol Dependence* 169:117–127.

Yee, A., M. C. Hoong, Y. C. Joyce, and H. S. Loh. 2018. Smoking cessation among methadone-maintained patients: A meta-analysis. *Substance Use & Misuse* 53(2):276–285.

Young, A. M., J. R. Havens, and C. G. Leukefeld. 2010. Route of administration for illicit prescription opioids: A comparison of rural and urban drug users. *Harm Reduction Journal* 7:24.

Zilberman, M. L., H. Tavares, S. B. Blume, and N. el-Guebaly. 2003. Substance use disorders: Sex differences and psychiatric comorbidities. *Canadian Journal of Psychiatry* 48(1):5–13.

Zur, J., J. Tolbert, J. Sharac, and A. Markus. 2018. *The role of community health centers in addressing the opioid epidemic*. Kaiser Family Foundation. https://www.kff.org/medicaid/issue-brief/the-role-of-community-health-centers-in-addressing-the-opioid-epidemic (accessed February 11, 2019).

4

Medications for Opioid Use Disorder in Various Treatment Settings

Medication-based treatment is effective across all treatment settings studied to date. Withholding or failing to have available all classes of U.S. Food and Drug Administration–approved medication for the treatment of opioid use disorder in any care or criminal justice setting is denying appropriate medical treatment.

Access to medications for treating opioid use disorder (OUD) is highly variable across different types of treatment settings. Figure 4-1 shows the density of substance use disorder (SUD) treatment facilities by county in the United States.[1] Although overall roughly 36 percent of SUD treatment facilities offer medication to patients (see Figure 4-2), only about 6 percent provide patients with a choice of all three U.S. Food and Drug Administration (FDA)-approved medications (amfAR, 2018; Mojtabai et al., 2019) (see Figure 4-3). This chapter reviews the evidence on differences in medication access and use in different treatment settings and, to the extent that it is available, any scientific rationale underpinning those differences.

OPIOID TREATMENT PROGRAMS

The Narcotic Addict Treatment Act of 1974[2] requires that methadone be administered to patients only through federally certified and regulated opioid treatment programs (OTPs), commonly referred to as methadone clinics. OTPs were originally created to provide methadone treatment, but today many of them also provide other medications for OUD. The Substance Abuse and Mental Health Services Administration (SAMHSA) began certifying OTPs in 2001, and between 2003 and 2015, the number of patients enrolled in methadone treatment increased by 57 percent.[3] After the introduction of buprenorphine in 2002, the number of OTPs offering buprenorphine increased from 11 percent (121 OTPs) in 2003 to 58 percent (779 OTPs) in 2015. The number of OTPs that offer extended-release naltrexone also grew from 11 percent of the total (125 OTPs) in 2011 to 23 percent (315 OTPs) in 2015 (Alderks, 2017).

All OTPs must be certified by SAMHSA and registered by the Drug Enforcement Administration (DEA). Before certification, an OTP must first be evaluated in a peer-review process by a SAMHSA-approved accrediting organization, which conducts site visits and reviews the facility's policies, procedures, and practices. Even after accreditation, an OTP is not formally certified to administer methadone until SAMHSA has determined that the OTP conforms with federal regulations regarding patient admission criteria, recordkeeping guidelines, and required services, such as counseling and testing for drug use. After certification, the OTP must also apply separately for registration with the DEA, which has requirements around security,

[1] Darker areas on the maps indicate a greater number of facilities (light purple = one facility; medium purple = two facilities; dark purple = three or more facilities). Note that counties differ in size—those in the Southwest tend to be much larger in area than counties in the Northeast, for example—and this may affect the interpretation of the maps.

[2] Public Law 93-281 (1974).

[3] This increase appears to stem from an increase in OTPs combined with better identification of OTPs in the National Survey of Substance Abuse Treatment Services survey (Alderks, 2017).

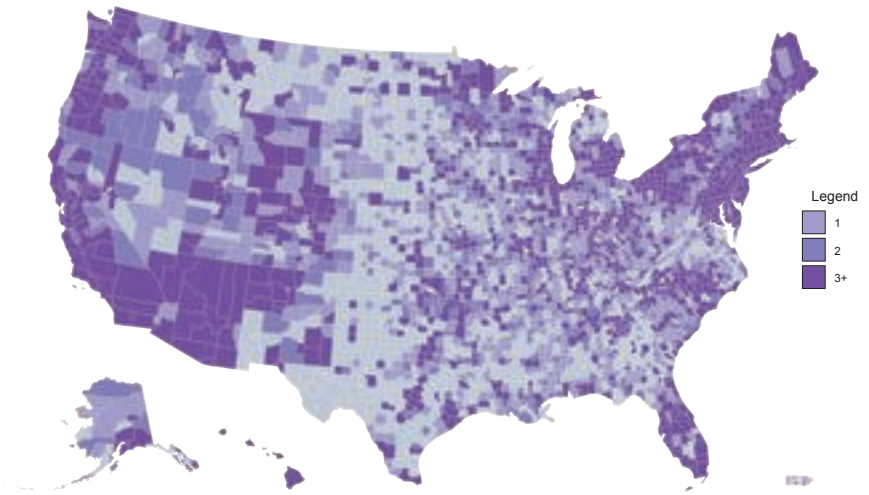


FIGURE 4-1 All substance use disorder treatment facilities, by county (2018).
NOTE: Gray = no facilities; light purple = one facility; medium purple = two facilities; dark purple = three or more facilities.
SOURCE: amfAR, 2018.

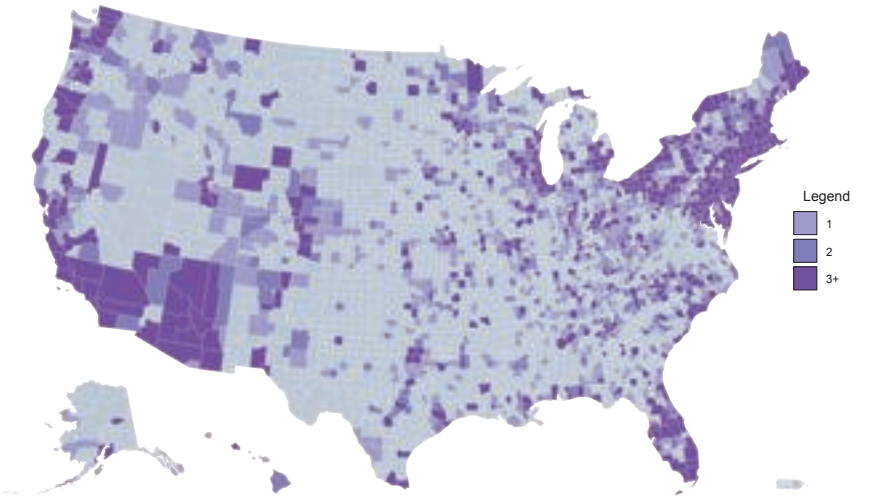


FIGURE 4-2 Substance use disorder treatment facilities offering medications for OUD, by county (2018).
NOTE: Gray = no facilities; light purple = one facility; medium purple = two facilities; dark purple = three or more facilities.
SOURCE: amfAR, 2018.

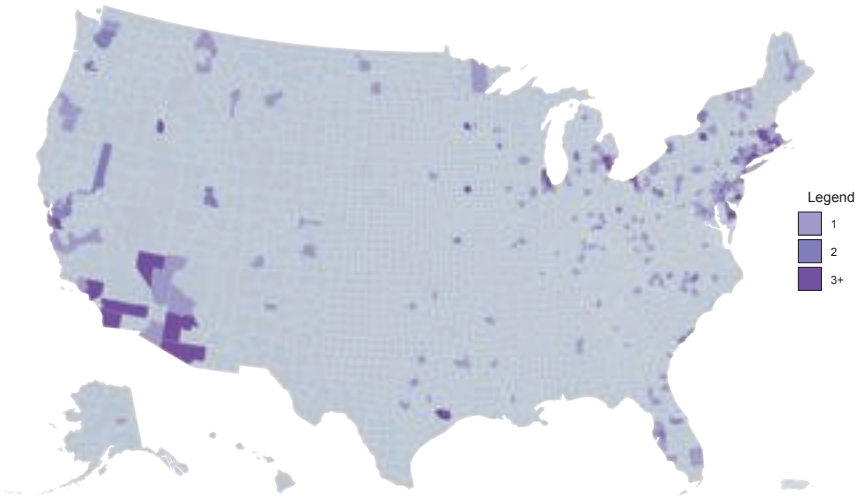


FIGURE 4-3 Substance use disorder treatment facilities offering all three medications for OUD, by county (2018).
NOTE: Gray = no facilities; light purple = one facility; medium purple = two facilities; dark purple = three or more facilities.
SOURCE: amfAR, 2018.

inventory, and recordkeeping. An OTP's registration from the DEA must be renewed on an annual basis (GAO, 2016). The regulations also require that most patients attend the clinic nearly every day to receive their doses of medication, which is an attempt to reduce diversion. See Chapter 5 for a detailed discussion on how some of the regulations around methadone are a barrier to treatment.

OFFICE-BASED OPIOID TREATMENT

Expanding the delivery of medications for OUD through medical office–based treatment settings has been a strategy for increasing access to medications for OUD (see Box 4-1). Currently, naltrexone can be prescribed by any physician, nurse practitioner (NP), or physician assistant (PA) within a scope of practice. In contrast, the Drug Addiction Treatment Act of 2000[4] stipulates that buprenorphine can only be prescribed by providers with additional DEA certification, unless they are working in an OTP setting. Moreover, to qualify for a waiver from the DEA to prescribe buprenorphine, federal law

[4] See 21 U.S.C. § 823(g)(2).

BOX 4-1
Office-Based Methadone Treatment

Office-based methadone treatment has been used in the United States since June 1983, when 25 methadone patients were admitted to an office-based program at The Rockefeller University in New York City (Novick et al., 1988). Several different pilot models of office-based methadone treatment soon followed in settings that included opioid treatment programs (OTPs) (San Francisco, California), pharmacies (Baltimore, Maryland), and physicians' offices (Sacramento, California, and rural New Hampshire).[a]

In 1997, the National Institute on Drug Abuse funded a 3-year office-based methadone treatment study in New York with 151 women enrolled. In this study, as in the other pilot models, the outcomes were not significantly different for patients receiving treatment in OTP settings versus those treated in office-based settings. This demonstrates that physicians in office-based settings can monitor patients as effectively as physicians working within the more complicated OTP regimens (Tuchman and Drucker, 2001). When interviewed, patients treated with methadone in office-based settings said that because they were not required to go to an OTP on a daily basis, they were able to pursue endeavors such as opening their own businesses and traveling for their professions (Salsitz et al., 2000).

Several different models of office-based methadone treatment have been tested in the United States and in other countries. One U.S. model involves close affiliation between the office-based practice and the OTP, with stable patients referred for office-based treatment and continued provision of ancillary treatment services through the OTP as needed. In this model, exemptions must be requested by OTPs, and office-based physicians must be affiliated with a sponsoring OTP. Patients are moved to office-based methadone treatment as a type of "graduation" from the OTP. One study reported a 98 percent retention rate among patients from a socioeconomically disadvantaged population who were selected to receive a monthly supply of methadone in an office setting (Harris et al., 2006).

European and Canadian models of office-based methadone treatment are significantly less restrictive. Patients may be admitted and entirely managed in the physician's office with periodic visits, drug testing, and medication management. In the Canadian model, for example, methadone is dispensed as frequently as daily from a collaborating pharmacy, and patients can participate in community-based psychosocial care. In such models, physicians work relatively independently of OTPs (ASAM, 2005).

---

[a] NYS OASAS (New York State Office of Alcoholism and Substance Abuse Services). 2002. Comparison of OBOT models. Interagency document.

requires that physicians take an 8-hour course and that NPs and PAs complete 24 hours of training. In addition, the number of patients that providers are allowed to treat is restricted. Specialist physicians are allowed to treat up to 100 patients in the first year and 275 patients thereafter, provided they have a waiver and meet additional criteria (e.g., board certification in addiction medicine or psychiatry), while NPs and PAs can treat no more than 100 patients each (SAMHSA, 2016, 2018a,b).

A systematic review of studies that assessed different primary care and specialty care models for delivering medication-based treatment for OUD did not reach any strong conclusions regarding which specific delivery models led to better patient outcomes (Lagisetty et al., 2017). However, the review did note that studies in which the treatment was successful, with high treatment retention and good-quality care measures, tended to use multidisciplinary care (i.e., specialty addiction services integrated with primary care) or coordinated care (i.e., physicians supported by care management).

In the United States, medications for treating OUD are typically delivered through high-threshold, low-tolerance models that require patients to comply with a number of strict requirements, such as frequent urine testing and weekly counseling sessions, in order to receive treatment. A patient's response in the first month of treatment is often predictive of longer-term response (Weiss and Rao, 2017). For example, patients who submit drug-positive urine specimens or miss their appointments early in treatment are usually associated with poorer outcomes. However, it has been argued that these requirements can have counterproductive effects on treatment outcomes (McElrath, 2018) and that lower-threshold models, which do not place additional requirements on individuals trying to access medication-based treatment, hold promise in lowering the bar for entry into treatment (Socias et al., 2018). Individualized treatment using measurement-based care can help support patients during the early stages of treatment. This involves repeatedly measuring variables and adapting treatment in response to a patient's progress or lack thereof. While this practice is widely used throughout medicine, it is used infrequently in the treatment of SUDs, including OUD (Trivedi and Daly, 2007).

Community health centers (CHCs) can also play an important role in improving access to OUD treatment among people who are medically underserved. A survey of CHCs found that many had expanded their OUD treatment services to respond to the escalating epidemic. Almost half of all CHCs offered at least one medication for OUD, and nearly two-thirds of the CHCs providing medication-based treatment offered at least two of the three FDA-approved medications. Buprenorphine, the most commonly prescribed medication for opioid withdrawal, was available at 87 percent of CHCs that provided any medication for OUD (Zur et al., 2018). How-

ever, many CHCs face ongoing challenges related to insufficient treatment capacity—63 percent reported that they did not have the capacity to treat all of their patients with OUD, and 68 percent of centers reported shortages of referral providers (Zur et al., 2018).

ACUTE CARE SETTINGS

The number of people treated for opioid-related conditions, including opioid overdose, in emergency departments and hospitals in the United States has increased substantially in recent years. Between the third quarter of 2016 and the third quarter of 2017, the number of emergency department visits for opioid overdoses increased almost 30 percent, according to data captured through the National Syndromic Surveillance Program of the U.S. Centers for Disease Control and Prevention (CDC) (Vivolo-Kantor et al., 2018). Furthermore, people with OUD are overrepresented in the population of hospitalized patients compared with their prevalence in the general population (Peterson et al., 2018). Therefore, acute care settings provide opportunities to intervene with patients who have OUD. Even though most providers in emergency departments and hospitals are not waivered to prescribe buprenorphine, non-waivered providers are permitted to administer buprenorphine or methadone to patients under their care for other medical reasons.[5]

Various studies indicate that effective medication-based treatment for OUD can be initiated in acute care settings and that patients can be successfully transferred to outpatient medication-based treatment after hospital discharge. The emergency department visit is a chance to treat people with OUD for withdrawal symptoms with medication and to bridge those patients to longer-term medication-based treatment plans (Chamberlin et al., 2018). For example, in one recent study, buprenorphine treatment initiated in the emergency department was associated with improved short-term treatment engagement and decreased illicit opioid use (D'Onofrio et al., 2015). In a randomized trial of hospitalized patients with OUD, patients who received an intervention that included induction, stabilization, and transitioning to long-term outpatient buprenorphine treatment had improved linkage to treatment after they were discharged compared with patients who received only a 5-day buprenorphine taper (Liebschutz et al., 2014). Although initiating treatment with methadone or buprenorphine in the hospital represents an important opportunity to engage patients in longer-term care, the rates of linkage to treatment after patients are discharged have been low (Naeger et al., 2016; Rosenthal and Goradia, 2017; Trowbridge et al., 2017). In one study, only 28 percent of opioid overdose

[5] Drug Addiction Treatment Act of 2000 (DATA 2000). See 21 U.S.C. § 823(g)(2).

survivors seen in an emergency department or hospital were afterward linked to medication-based treatment for OUD (Larochelle et al., 2018).

OTHER CARE SETTINGS

Other care settings that could provide or enable access to medication-based treatment for OUD include residential facilities, nursing homes, outpatient facilities, supportive housing, and homeless shelters. More than 500,000 people with OUD in 2016 entered these care settings,[6] many of which focus primarily on "cold turkey" detoxification and impose a zero-tolerance policy for opioid use of any kind—with no exception for evidence-based medications like methadone and buprenorphine. The continued popularity of treatment settings that ban or discourage medication persists despite the lack of evidence for this approach and the known potential for harmful effects (NARR, 2018). Return-to-use rates following medically supervised withdrawal (also known as "detox") have been reported to be as high as 65 to 91 percent; this approach also carries a high risk of overdose due to a reduced tolerance for opioids if patients return to use (Broers et al., 2000; Chutuape et al., 2001). Many funding streams for these facilities are tied to the criminal justice system or housing authorities, creating strong incentives to steer patients toward non-medication-based treatment approaches (Andersen and Kallestrup, 2018).

CRIMINAL JUSTICE SETTINGS

While OUD is highly prevalent in criminal justice settings in the United States, few justice-involved individuals can access medication-based treatment while in jail or prison. In addition, justice settings rarely have systems in place to transition individuals with OUD to medication-based treatment at the time of release. More than half of the people in U.S. prisons have a diagnosis of SUD with or without co-occurring serious mental illness,[7] with the rate of OUD in jails and prisons estimated to be around 15 percent (Baillargeon et al., 2009; James and Glaze, 2006; Peters et al., 1998).

[6] Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration, Treatment Episode Data Set.

[7] People with OUD in criminal justice settings often have co-occurring psychiatric disorders, they tend to have high rates of infectious diseases such as HIV and hepatitis C virus, and they often face complex challenges related to emotional, physical, social, and financial issues (Brochu et al., 1999). Although criminal justice populations tend to be male, increasing numbers of women are entering the system. Many of these women face even more severe issues than their male counterparts in terms of social, financial, emotional, and medical obstacles, which are compounded by an increased likelihood of a history of abuse (Langan and Pelissier, 2001).

A 2007–2009 summary from the Bureau of Justice Statistics indicated that 58 percent of state prisoners and 63 percent of sentenced jail inmates met the criteria for a SUD, versus around 5 percent of the total adult population in the country (Bronson et al., 2017). However, only around 28 percent of prisoners and 22 percent of jail inmates participated in a drug treatment program (Bronson et al., 2017). Using 2014 National Treatment Episode Data Set data, Krawczyk and colleagues examined the use of methadone and buprenorphine treatment among people referred through the judicial system to specialty treatment for OUD; only 4.6 percent of justice-referred clients received either medication (Krawczyk et al., 2017). A survey of 51 prison systems across the country found great variation by state, but, overall, most corrections systems do not offer any medication to incarcerated individuals with OUD, nor do they provide referral to treatment upon release (Nunn et al., 2009). Methadone was available in about half of the systems surveyed, but around half of those facilities limited methadone treatment to pregnant women or for chronic pain management; only 14 percent of systems provided buprenorphine. Few prison systems offered all three medications as treatment options for OUD (Nunn et al., 2009).

For people with OUD involved with the criminal justice system, a lack of access to medication-based treatment leads to a greater risk of returning to use and overdose after they are released from incarceration (Chandler et al., 2016). People with a history of OUD have a demonstrably high risk of mortality following release from incarceration. One study found an all-cause mortality rate of 737 per 100,000 person-years among former prisoners, with opioids related to almost 15 percent of all deaths (Binswanger et al., 2013). In a randomized trial of participants already receiving methadone treatment at arrest, those who were forced to withdraw from methadone were less likely to resume methadone treatment after release (Rich et al., 2015). Another retrospective cohort analysis examined the implementation of a comprehensive medication-based treatment program in the Rhode Island corrections systems. Results indicated a 60.5 percent reduction in the proportion of all overdose deaths of people who had recently been incarcerated following release, relative to the proportion of overdose deaths in the period before the program was initiated (Green et al., 2018). Randomized trials have also compared the outcomes of people who initiate methadone treatment prior to release from incarceration versus those who were referred to treatment upon release. Participants who initiated treatment while incarcerated were more likely to engage in treatment after release, and they reported less illicit drug use after 6 months (McKenzie et al., 2012). A recent meta-analysis of experimental and quasi-experimental studies examining provision of medications for OUD in correctional settings found that methadone significantly improved engagement in treatment postrelease, reduced illicit use, and

use by injection; however, reductions in recidivism were not consistently observed (Moore et al., 2019), likely due to state differences in probation and parole, among others. The authors noted too few experimental studies involving buprenorphine (n = 3) and naltrexone (n = 3) to perform meta-analysis of the data for these outcomes. Nevertheless, critical review of the individual studies indicated that buprenorphine and naltrexone were either superior to placebo or to methadone, or were comparable to methadone in reducing illicit use postrelease (Moore et al., 2019). Researchers at three study sites in the Studies on Medications for Addiction Treatment in Correctional Settings collaborative are pooling data from randomized effectiveness trials comparing extended-release naltrexone to methadone with enhanced treatment among people with OUD who are incarcerated; they are also looking at the benefits of a patient navigation program when added to medication (Chandler et al., 2016). Given their impact on mortality, it has been argued that withholding medications for OUD during incarceration is unethical, as would be withholding insulin or blood pressure medication (Bruce and Schleifer, 2008).

Civil commitment is not incarceration, but its alignment with the court system creates important considerations related to people with OUD and their access to medication-based treatment. The practice of civil commitment for opioid use is a legal provision that permits a judge to mandate opioid treatment (typically to an inpatient setting) for individuals whose opioid use poses a high likelihood of serious harm to self or to others, such as overdose, incapacitation, or other substantial danger (Christopher et al., 2015). A majority of U.S. states permit civil commitment for SUDs, and the use of civil commitments has been increasing in recent years (Cavaiola and Dolan, 2016). Like other criminal justice practices involving people with OUD, civil commitment procedures typically do not involve the provision of medication-based treatment, and research demonstrates high rates both of return to use and of overdose postcommitment under these practices. Postcommitment remission rates can be improved by a number of factors, including postcommitment medication-based treatment (Christopher et al., 2018).

According to one study, 56 percent of drug courts refer to treatment programs that offer at least one type of medication for OUD (Matusow et al., 2013). However, many of those programs require that medications be used only for tapering or as a bridge to completely stopping opioid use of any kind, including methadone or buprenorphine; this is not consistent with the evidence base for the most effective treatment strategy for OUD. A number of recent studies have found support for the use of injectable naltrexone in criminal justice settings. Despite the high discontinuation rates for injectable naltrexone, it may be more acceptable to judges and other correctional officials than methadone or buprenorphine (Lee et al.,

2015, 2016; Lincoln et al., 2018). Notably, when all three FDA-approved medications are available, only a small number of incarcerated patients select naltrexone (Green et al., 2018).

INNOVATIVE SETTINGS FOR OUD TREATMENT

Expanding treatment to settings outside of the medical and specialty addiction sectors has the potential to increase treatment access for traditionally hard-to-reach and socially disenfranchised populations. A broader definition of treatment settings may be necessary to connect people with medications in those populations, which include people who have never previously engaged in treatment, people who inject drugs, people who have severe OUD, people who are homeless, people who have recently been released from jails or prisons, and people who have other conditions that may make it challenging to access treatment (Hall et al., 2014). Examples of innovative treatment settings include

- mobile medication units to provide medication-based treatment directly to people's homes or communities (Gordon et al., 2017; Torrens et al., 2013);
- group-based treatment to homeless individuals (Doorley et al., 2017);
- treatment within syringe exchange programs (Bachhuber et al., 2018; Fox et al., 2015; Kuo et al., 2003);
- physician–pharmacist collaborative models (DiPaula and Menachery, 2015); and
- low-threshold "transitions clinics" or methadone linkage programs for people recently released from jail or prison (Fox et al., 2014; Rich et al., 2005).

The "hub and spoke" model, which involves collaborative care provided through coordinated treatment across OTPs to office-based outpatient treatment, offers another innovative approach to improved care integration (Brooklyn and Sigmon, 2017). Although new treatment strategies are emerging for connecting hard-to-reach populations with OUD to medication-based treatment, few of these have been rigorously tested.

Low-Barrier Medication-Based Treatment

Policies and protocols that create more accessible medication-based treatment are generally referred to as low-barrier medication-based treatment. Emerging research suggests that there are a range of benefits associated with low-barrier approaches to providing medications for OUD. Such

approaches include interim methadone dosing, which is the provision of methadone medication to patients who are not yet fully enrolled into a comprehensive methadone program (Schwartz et al., 2011), and buprenorphine home induction protocols (Bhatraju et al., 2017; Cunningham et al., 2011; Gunderson et al., 2010; Lee et al., 2009). Other new low-barrier approaches are novel models with promising evidence of benefits such as successful naloxone distribution and improved uptake of medication-based treatment. For instance, one study carried out in the fentanyl-affected city of Vancouver used a modified mobile trailer located near an emergency department to provide a post-overdose care alternative, documenting a substantial number of medication-based treatment inductions on site (Scheuermeyer et al., 2018). Research in these areas is needed to better meet the needs of more patients and to quantify the benefit, risk, and cost-effectiveness of these approaches to medication-based treatment delivery.

Technological Tools

The incorporation of electronic health records (EHRs) into many treatment systems can be leveraged to support research and to better understand proficiencies in clinical services related to the provision of medication-based treatment for OUD. Clinical dashboards that are populated from EHR systems provide real-time actionable data, for example, which would be highly valuable for the treatment of OUD. In a recent review of the use of clinical dashboards, Dowding and colleagues concluded that clinicians' immediate access to information can improve adherence to quality standards and help improve patient outcomes (Dowding et al., 2015; Patterson Silver Wolf, 2018). While technology advancements in behavioral health hold promise in the treatment of OUD, these tools need to be underpinned by a sound body of evidence assessing their impact on the access, quality, and cost of OUD treatment services from well-controlled randomized clinical trials (Ramsey, 2015). Telemedicine represents another potential opportunity to reach patients in underserved areas as well as to link providers who are inexperienced in treating OUD with mentors (Huhn and Dunn, 2017; Weintraub et al., 2018).

Conclusion 6:
Medication-based treatment is effective across all treatment settings studied to date. Withholding or failing to have available all classes of U.S. Food and Drug Administration–approved medication for the treatment of opioid use disorder in any care or criminal justice setting is denying appropriate medical treatment.

Treatment with FDA-approved medications is clearly effective in a broader range of care settings (e.g., office-based care settings, acute care, and criminal justice settings) than is currently the norm. There is no scientific evidence that justifies withholding medications from OUD patients in any setting or denying social services (e.g., housing, income supports) to individuals on medication for OUD. Therefore, to withhold treatment or deny services under these circumstances is unethical.

REFERENCES

Alderks, C. E. 2017. *Trends in the use of methadone, buprenorphine, and extended-release naltrexone at substance abuse treatment facilities: 2003–2015 (update)*. https://www.samhsa.gov/data/sites/default/files/report_3192/ShortReport-3192.html (accessed February 12, 2019).

amfAR (The Foundation for AIDS Research). 2018. *National opioid epidemic: Facilities providing substance abuse services*. http://opioid.amfar.org/indicator/SA_fac (accessed January 15, 2019).

Andersen, K. J., and C. M. Kallestrup. 2018. Rejected by A. A. *The New Republic*, June 27.

ASAM (American Society of Addiction Medicine). 2005. *Public policy statement on office-based opioid agonist treatment (OBOT)*. https://www.asam.org/advocacy/find-a-policy-statement/view-policy-statement/public-policy-statements/2011/12/15/office-based-opioid-agonist-treatment-(obot) (accessed February 12, 2019).

Bachhuber, M. A., C. Thompson, A. Prybylowski, J. Benitez, S. Mazzella, and D. Barclay. 2018. Description and outcomes of a buprenorphine maintenance treatment program integrated within Prevention Point Philadelphia, an urban syringe exchange program. *Substance Abuse* 39(2):167–172.

Baillargeon, J., T. P. Giordano, J. D. Rich, Z. H. Wu, K. Wells, B. H. Pollock, and D. P. Paar. 2009. Accessing antiretroviral therapy following release from prison. *JAMA* 301(8):848–857.

Bhatraju, E. P., E. Grossman, B. Tofighi, J. McNeely, D. DiRocco, M. Flannery, A. Garment, K. Goldfeld, M. N. Gourevitch, and J. D. Lee. 2017. Public sector low threshold office-based buprenorphine treatment: Outcomes at year 7. *Addiction Science & Clinical Practice* 12(1):7.

Binswanger, I. A., P. J. Blatchford, S. R. Mueller, and M. F. Stern. 2013. Mortality after prison release: Opioid overdose and other causes of death, risk factors, and time trends from 1999 to 2009. *Annals of Internal Medicine* 159(9):592–600.

Brochu, S., L. Guyon, and L. Desjardins. 1999. Comparative profiles of addicted adult populations in rehabilitation and correctional services. *Journal of Substance Abuse Treatment* 16(2):173–182.

Broers, B., F. Giner, P. Dumont, and A. Mino. 2000. Inpatient opiate detoxification in Geneva: Follow-up at 1 and 6 months. *Drug and Alcohol Dependence* 58(1–2):85–92.

Bronson, J., J. Stroop, S. Zimmer, and M. Berzofsky. 2017. *Drug use, dependence, and abuse among state prisoners and jail inmates, 2007–2009*. Washington, DC: U.S. Department of Justice, Bureau of Justice Statistics.

Brooklyn, J. R., and S. C. Sigmon. 2017. Vermont hub-and-spoke model of care for opioid use disorder: Development, implementation, and impact. *Journal of Addiction Medicine* 11(4):286–292.

Bruce, R. D., and R. A. Schleifer. 2008. Ethical and human rights imperatives to ensure medication-assisted treatment for opioid dependence in prisons and pre-trial detention. *International Journal on Drug Policy* 19(1):17–23.

Cavaiola, A. A., and D. Dolan. 2016. Considerations in civil commitment of individuals with substance use disorders. *Substance Abuse* 37(1):181–187.

Chamberlin, M., A. Herring, J. Luftig, M. Glenn. 2018. *Treating opioid withdrawal in the ED with buprenorphine: A bridge to recovery*. https://www.aliem.com/2018/05/treating-opioid-withdrawal-buprenorphine (accessed January 3, 2019).

Chandler, R. K., M. S. Finger, D. Farabee, R. P. Schwartz, T. Condon, L. J. Dunlap, G. A. Zarkin, K. McCollister, R. D. McDonald, E. Laska, D. Bennett, S. M. Kelly, M. Hillhouse, S. G. Mitchell, K. E. O'Grady, and J. D. Lee. 2016. The SOMATICS collaborative: Introduction to a National Institute on Drug Abuse cooperative study of pharmacotherapy for opioid treatment in criminal justice settings. *Contemporary Clinical Trials* 48:166–172.

Christopher, P. P., D. A. Pinals, T. Stayton, K. Sanders, and L. Blumberg. 2015. Nature and utilization of civil commitment for substance abuse in the United States. *Journal of the American Academy of Psychiatry and Law* 43(3):313–320.

Christopher, P. P., B. Anderson, and M. D. Stein. 2018. Civil commitment experiences among opioid users. *Drug and Alcohol Dependence* 193:137–141.

Chutuape, M. A., D. R. Jasinski, M. I. Fingerhood, and M. L. Stitzer. 2001. One-, three-, and six-month outcomes after brief inpatient opioid detoxification. *American Journal of Drug and Alcohol Abuse* 27(1):19–44.

Cunningham, C. O., A. Giovanniello, X. Li, H. V. Kunins, R. J. Roose, and N. L. Sohler. 2011. A comparison of buprenorphine induction strategies: Patient-centered home-based inductions versus standard-of-care office-based inductions. *Journal of Substance Abuse Treatment* 40(4):349–356.

DiPaula, B. A., and E. Menachery. 2015. Physician–pharmacist collaborative care model for buprenorphine-maintained opioid-dependent patients. *Journal of the American Pharmacists Association* 55(2):187–192.

D'Onofrio, G., P. G. O'Connor, M. V. Pantalon, M. C. Chawarski, S. H. Busch, P. H. Owens, S. L. Bernstein, and D. A. Fiellin. 2015. Emergency department–initiated buprenorphine/naloxone treatment for opioid dependence: A randomized clinical trial. *JAMA* 313(16):1636–1644.

Doorley, S. L., C. J. Ho, E. Echeverria, C. Preston, H. Ngo, A. Kamal, and C. O. Cunningham. 2017. Buprenorphine shared medical appointments for the treatment of opioid dependence in a homeless clinic. *Substance Abuse* 38(1):26–30.

Dowding, D., R. Randell, P. Gardner, G. Fitzpatrick, P. Dykes, J. Favela, S. Hamer, Z. Whitewood-Moores, N. Hardiker, E. Borycki, and L. Currie. 2015. Dashboards for improving patient care: Review of the literature. *International Journal of Medical Informatics* 84(2):87–100.

Fox, A. D., M. R. Anderson, G. Bartlett, J. Valverde, J. L. Starrels, and C. O. Cunningham. 2014. Health outcomes and retention in care following release from prison for patients of an urban post-incarceration transitions clinic. *Journal of Health Care for the Poor and Underserved* 25(3):1139–1152.

Fox, A. D., A. Chamberlain, T. Frost, and C. O. Cunningham. 2015. Harm reduction agencies as a potential site for buprenorphine treatment. *Substance Abuse* 36(2):155–160.

GAO (U.S. Government Accountability Office). 2016. *Opioid addiction: Laws, regulations, and other factors can affect medication-assisted treatment access*. Washington, DC: U.S. Government Accountability Office. https://www.gao.gov/assets/690/680050.pdf (accessed February 12, 2019).

Gordon, M. S., F. J. Vocci, T. T. Fitzgerald, K. E. O'Grady, and C. P. O'Brien. 2017. Extended-release naltrexone for pre-release prisoners: A randomized trial of medical mobile treatment. *Contemporary Clinical Trials* 53:130–136.

Green, T. C., J. Clarke, L. Brinkley-Rubinstein, B. D. L. Marshall, N. Alexander-Scott, R. Boss, and J. D. Rich. 2018. Postincarceration fatal overdoses after implementing medications for addiction treatment in a statewide correctional system. *JAMA Psychiatry* 75(4):405–407.

Gunderson, E. W., X. Q. Wang, D. A. Fiellin, B. Bryan, and F. R. Levin. 2010. Unobserved versus observed office buprenorphine/naloxone induction: A pilot randomized clinical trial. *Addictive Behaviors* 35(5):537–540.

Hall, G., C. J. Neighbors, J. Iheoma, S. Dauber, M. Adams, R. Culleton, F. Muench, S. Borys, R. McDonald, and J. Morgenstern. 2014. Mobile opioid agonist treatment and public funding expands treatment for disenfranchised opioid-dependent individuals. *Journal of Substance Abuse Treatment* 46(4):511–515.

Harris, K. A., Jr., J. H. Arnsten, H. Joseph, J. Hecht, I. Marion, P. Juliana, and M. N. Gourevitch. 2006. A 5-year evaluation of a methadone medical maintenance program. *Journal of Substance Abuse Treatment* 31(4):433–438.

Huhn, A. S., and K. E. Dunn. 2017. Why aren't physicians prescribing more buprenorphine? *Journal of Substance Abuse Treatment* 78:1–7.

James, D. J., and L. E. Glaze. 2006. *Mental health problems of prison and jail inmates*. Washington, DC: U.S. Department of Justice, Office of Justice Programs, Bureau of Justice Statistics.

Krawczyk, N., C. E. Picher, K. A. Feder, and B. Saloner. 2017. Only one in twenty justice-referred adults in specialty treatment for opioid use receive methadone or buprenorphine. *Health Affairs* 36(12):2046–2053.

Kuo, I., J. Brady, C. Butler, R. Schwartz, R. Brooner, D. Vlahov, and S. A. Strathdee. 2003. Feasibility of referring drug users from a needle exchange program into an addiction treatment program: Experience with a mobile treatment van and LAAM maintenance. *Journal of Substance Abuse Treatment* 24(1):67–74.

Lagisetty, P., K. Klasa, C. Bush, M. Heisler, V. Chopra, and A. Bohnert. 2017. Primary care models for treating opioid use disorders: What actually works? A systematic review. *PLOS ONE* 12(10):e0186315.

Langan, N. P., and B. M. Pelissier. 2001. Gender differences among prisoners in drug treatment. *Journal of Substance Abuse* 13(3):291–301.

Larochelle, M. R., D. Bernson, T. Land, T. J. Stopka, N. Wang, Z. Xuan, S. M. Bagley, J. M. Liebschutz, and A. Y. Walley. 2018. Medication for opioid use disorder after nonfatal opioid overdose and association with mortality: A cohort study. *Annals of Internal Medicine* 169(3):137–145.

Lee, J. D., E. Grossman, D. DiRocco, and M. N. Gourevitch. 2009. Home buprenorphine/naloxone induction in primary care. *Journal of General Internal Medicine* 24(2):226–232.

Lee, J. D., P. D. Friedmann, T. Y. Boney, R. A. Hoskinson, Jr., R. McDonald, M. Gordon, M. Fishman, D. T. Chen, R. J. Bonnie, T. W. Kinlock, E. V. Nunes, J. W. Cornish, and C. P. O'Brien. 2015. Extended-release naltrexone to prevent relapse among opioid dependent, criminal justice system involved adults: Rationale and design of a randomized controlled effectiveness trial. *Contemporary Clinical Trials* 41:110–117.

Lee, J. D., P. D. Friedmann, T. W. Kinlock, E. V. Nunes, T. Y. Boney, R. A. Hoskinson, Jr., D. Wilson, R. McDonald, J. Rotrosen, M. N. Gourevitch, M. Gordon, M. Fishman, D. T. Chen, R. J. Bonnie, J. W. Cornish, S. M. Murphy, and C. P. O'Brien. 2016. Extended-release naltrexone to prevent opioid relapse in criminal justice offenders. *New England Journal of Medicine* 374(13):1232–1242.

Liebschutz, J. M., D. Crooks, D. Herman, B. Anderson, J. Tsui, L. Z. Meshesha, S. Dossabhoy, and M. Stein. 2014. Buprenorphine treatment for hospitalized, opioid-dependent patients: A randomized clinical trial. *JAMA Internal Medicine* 174(8):1369–1376.

Lincoln, T., B. D. Johnson, P. McCarthy, and E. Alexander. 2018. Extended-release naltrexone for opioid use disorder started during or following incarceration. *Journal of Substance Abuse Treatment* 85:97–100.

Matusow, H., S. L. Dickman, J. D. Rich, C. Fong, D. M. Dumont, C. Hardin, D. Marlowe, and A. Rosenblum. 2013. Medication assisted treatment in U.S. drug courts: Results from a nationwide survey of availability, barriers and attitudes. *Journal of Substance Abuse Treatment* 44(5):473–480.

McElrath, K. 2018. Medication-assisted treatment for opioid addiction in the United States: Critique and commentary. *Substance Use & Misuse* 53(2):334–343.

McKenzie, M., N. Zaller, S. L. Dickman, T. C. Green, A. Parihk, P. D. Friedmann, and J. D. Rich. 2012. A randomized trial of methadone initiation prior to release from incarceration. *Substance Abuse* 33(1):19–29.

Mojtabai, R., C. Mauro, M. M. Wall, C. L. Barry, and M. Olfson. 2019. Medication treatment for opioid use disorders in substance use treatment facilities. *Health Affairs* 38(1):14–23.

Moore, K. E., W. Roberts, H. H. Reid, K. M. Z. Smith, L. M. S. Oberleitner, and S. A. McKee. 2019. Effectiveness of medication assisted treatment for opioid use in prison and jail settings: A meta-analysis and systematic review. *Journal of Substance Abuse Treatment* 99:32–43.

Naeger, S., R. Mutter, M. M. Ali, T. Mark, and L. Hughey. 2016. Post-discharge treatment engagement among patients with an opioid-use disorder. *Journal of Substance Abuse Treatment* 69:64–71.

NARR (National Alliance for Recovery Residences). 2018. *MAT capable recovery residences: How state policy makers can enhance and expand capacity to adequately support medication assisted recovery*. https://narronline.org/wp-content/uploads/2018/09/NARR_MAT_guide_for_state_agencies.pdf (accessed February 28, 2019).

Novick, D. M., E. F. Pascarelli, H. Joseph, E. A. Salstiz, B. L. Richman, D. C. Des Jarlais, M. Anderson, V. P. Dole, and M. E. Nyswander. 1988. Methadone maintenance patients in general medical practice: A preliminary report. *JAMA* 259(22):3299–3302.

Nunn, A., N. Zaller, S. Dickman, C. Trimbur, A. Nijhawan, and J. D. Rich. 2009. Methadone and buprenorphine prescribing and referral practices in U.S. prison systems: Results from a nationwide survey. *Drug and Alcohol Dependence* 105(1–2):83–88.

Patterson Silver Wolf, D. A. 2018. The new social work. *Journal of Evidence-Informed Social Work* 15(6):695–706.

Peters, R. H., P. E. Greenbaum, J. F. Edens, C. R. Carter, and M. M. Ortiz. 1998. Prevalence of DSM-IV substance abuse and dependence disorders among prison inmates. *American Journal of Drug and Alcohol Abuse* 24(4):573–587.

Peterson, C., L. Xu, C. A. Mikosz, C. Florence, and K. A. Mack. 2018. U.S. hospital discharges documenting patient opioid use disorder without opioid overdose or treatment services, 2011–2015. *Journal of Substance Abuse Treatment* 92:35–39.

Ramsey, A. 2015. Integration of technology-based behavioral health interventions in substance abuse and addiction services. *International Journal of Mental Health and Addiction* 13(4):470–480.

Rich, J. D., M. McKenzie, D. C. Shield, F. A. Wolf, R. G. Key, M. Poshkus, and J. Clarke. 2005. Linkage with methadone treatment upon release from incarceration: A promising opportunity. *Journal of Addictive Diseases* 24(3):49–59.

Rich, J. D., M. McKenzie, S. Larney, J. B. Wong, L. Tran, J. Clarke, A. Noska, M. Reddy, and N. Zaller. 2015. Methadone continuation versus forced withdrawal on incarceration in a combined U.S. prison and jail: A randomised, open-label trial. *Lancet* 386(9991):350–359.

Rosenthal, R. N., and V. V. Goradia. 2017. Advances in the delivery of buprenorphine for opioid dependence. *Drug Design, Development and Therapy* 11:2493–2505.

Salsitz, E. A., H. Joseph, B. Frank, J. Perez, B. L. Richman, N. Salomon, M. F. Kalin, and D. M. Novick. 2000. Methadone medical maintenance (MMM): Treating chronic opioid dependence in private medical practice—A summary report (1983–1998). *Mount Sinai Journal of Medicine* 67(5–6):388–397.

SAMHSA (Substance Abuse and Mental Health Services Administration). 2016. Reports of the Surgeon General. In *Facing addiction in America: The Surgeon General's report on alcohol, drugs, and health*. Washington, DC: U.S. Department of Health and Human Services.

SAMHSA. 2018a. *Buprenorphine training for physicians*. https://www.samhsa.gov/medication-assisted-treatment/training-resources/buprenorphine-physician-training (accessed January 15, 2019).

SAMHSA. 2018b. *Qualify for nurse practitioners (NPs) and physician assistants (PAs) waiver*. https://www.samhsa.gov/programs-campaigns/medication-assisted-treatment/training-materials-resources/qualify-np-pa-waivers (accessed January 15, 2019).

Scheuermeyer, F. X., E. Grafstein, J. Buxton, K. Ahamad, M. Lysyshyn, S. DeVlaming, G. Prinsloo, C. Van Veen, A. Kestler, and R. Gustafson. 2018. Safety of a modified community trailer to manage patients with presumed fentanyl overdose. *Journal of Urban Health*, October 15 [Epub ahead of print].

Schwartz, R. P., S. M. Kelly, K. E. O'Grady, D. Gandhi, and J. H. Jaffe. 2011. Interim methadone treatment compared to standard methadone treatment: 4-month findings. *Journal of Substance Abuse Treatment* 41(1):21–29.

Socias, M. E., E. Wood, T. Kerr, S. Nolan, K. Hayashi, E. Nosova, J. Montaner, and M. J. Milloy. 2018. Trends in engagement in the cascade of care for opioid use disorder, Vancouver, Canada, 2006–2016. *Drug and Alcohol Dependence* 189:90–95.

Torrens, M., F. Fonseca, C. Castillo, and A. Domingo-Salvany. 2013. Methadone maintenance treatment in Spain: The success of a harm reduction approach. *Bulletin of the World Health Organization* 91(2):136–141.

Trivedi, M. H., and E. J. Daly. 2007. Measurement-based care for refractory depression: A clinical decision support model for clinical research and practice. *Drug and Alcohol Dependence* 88(Suppl 2):S61–S71.

Trowbridge, P., Z. M. Weinstein, T. Kerensky, P. Roy, D. Regan, J. H. Samet, and A. Y. Walley. 2017. Addiction consultation services—Linking hospitalized patients to outpatient addiction treatment. *Journal of Substance Abuse Treatment* 79:1–5.

Tuchman, E., and E. Drucker. 2001. *MMT & beyond—Office-based methadone prescribing*. http://www.methadone.org/downloads/documents/atf_2001_mmt_&_beyond.pdf (accessed February 12, 2019).

Vivolo-Kantor, A. M., P. Seth, R. M. Gladden, C. L. Mattson, G. T. Baldwin, A. Kite-Powell, and M. A. Coletta. 2018. Vital signs: Trends in emergency department visits for suspected opioid overdoses—United States, July 2016–September 2017. *Morbidity and Mortality Weekly Report* 67(9):279–285.

Weintraub, E., A. D. Greenblatt, J. Chang, S. Himelhoch, and C. Welsh. 2018. Expanding access to buprenorphine treatment in rural areas with the use of telemedicine. *American Journal of Addiction* 27(8):612–617.

Weiss, R. D., and V. Rao. 2017. The prescription opioid addiction treatment study: What have we learned. *Drug and Alcohol Dependence* 173(Suppl 1):S48–S54.

Zur, J., J. Tolbert, J. Sharac, and A. Markus. 2018. *The role of community health centers in addressing the opioid epidemic*. Kaiser Family Foundation. https://www.kff.org/medicaid/issue-brief/the-role-of-community-health-centers-in-addressing-the-opioid-epidemic (accessed February 12, 2019).

5

Barriers to Broader Use of Medications to Treat Opioid Use Disorder

Confronting the major barriers to the use of medications to treat opioid use disorder is critical to addressing the opioid crisis.

Despite the strong evidence for the effectiveness of medications in reducing morbidity and mortality, increasing treatment retention, and improving well-being for individuals with opioid use disorder (OUD), numerous barriers prevent broader access to medication-based treatment. According to 2019 estimates, less than 35 percent of adults with OUD had received treatment for opioid use in the past year (Jones and McCance-Katz, 2019), and no national data sources are currently available to precisely estimate the share of those patients who are being treated with one of the three U.S. Food and Drug Administration (FDA)-approved medications. Furthermore, national estimates indicate that there is usually a gap of several years between the onset of OUD and entering treatment. The delay between disease onset and initial treatment receipt has been estimated to be, on average, in the range of 4 to 7 years (Blanco et al., 2013; Wang et al., 2005). The barriers preventing broader access to life-saving medications for OUD include stigma, inadequate professional education and training related to the evidence base for using medication, and challenges in connecting individuals with medication-based treatment due to delivery system fragmentation, regulatory and legal barriers, barriers related to public and private health insurance coverage, and reimbursement and payment policies that do not incentivize the provision of high-value care for OUD. A critical unanswered question is which interventions or policy changes would be most likely to drive real system-level changes to increase access and use of medication-based treatment for people with OUD?

STIGMA

There are high levels of stigma toward individuals with OUD and toward medications to treat OUD both among the general public and among professionals in key sectors that commonly interact with individuals with OUD. This stigma poses significant barriers to the uptake of medication-based treatment. According to Link and Phelan (2001, p. 377), "stigma exists when elements of labeling, stereotyping, separation, status loss and discrimination occur together in a power situation that allows them." While some definitions of stigma do not include discrimination, in this report, we conceptualize stigma based on Link and Phelan's reasoning that the term stigma cannot hold the meaning we commonly assign to it when the concept of discrimination is not included. According to Link and Phelan (2001, p. 371), people are stigmatized when "the fact that they are labeled, set apart and linked to undesirable characteristics leads them to experience status loss and discrimination," thereby affecting their life prospects including income, education, housing status, and well-being. National public opinion data indicate that negative attitudes toward individuals with prescription OUD exceed those reported for other medical conditions, including mental

illness (Barry et al., 2014). More than three-quarters of respondents in a 2016 national survey reported viewing individuals with OUD as to blame for their substance use, and nearly three-quarters of respondents characterized people with OUD as lacking self-discipline (Kennedy-Hendricks et al., 2017). Two-thirds of respondents were unwilling to have a person with a drug use disorder marry into their family, and a majority endorsed discriminatory measures, such as allowing employers to deny employment to a person with OUD (Kennedy-Hendricks et al., 2017). Individuals who had personal experience with OUD—for example, having a family member or close friend with OUD—reported equally negative or more negative attitudes toward the disorder than the general public (Kennedy-Hendricks et al., 2017). This is notable because it differs from research on stigma toward people with mental illness (Alexander and Link, 2003; Corrigan et al., 2012; Couture and Penn, 2003; McSween, 2002), which generally finds personal experience with mental illness to be associated with less negative attitudes. Higher levels of stigma were also associated with greater support among the public for more punitive policy responses to the opioid epidemic (e.g., arresting and prosecuting people who obtain multiple prescriptions from different doctors) and lower support for public health–oriented policy responses (e.g., expanding Medicaid insurance benefits to cover OUD treatment) (Kennedy-Hendricks et al., 2016b).

Stigma toward people with OUD and toward people with substance use disorders (SUDs) more broadly is intertwined with persistent stigma (including labeling, stereotyping, status loss, and discrimination) that occurs on the basis of race and social class in the United States. Historically, U.S. drug policies have disproportionately targeted already marginalized groups (Morone, 1997; Singer and Page, 2014). For instance, early restrictions on opium were implemented during a period of heightened xenophobia toward Chinese immigrants (Morone, 1997). Studies have also focused attention on race-based stigma and discrimination directed toward African Americans as a profound legacy of the war on drugs (Capitanio and Herek, 1999; Kulesza et al., 2013; Minior et al., 2003; Semple et al., 2005). An analysis of a small sample of news media published between 2001 and 2011 found that white non-urban people with prescription OUDs were represented more sympathetically than non-white urban people with heroin use disorder (Netherland and Hansen, 2016). Substance use is often featured in media representations of economically disadvantaged populations (Bullock et al., 2001; Singer and Page, 2014). By tying populations that are already disenfranchised to substance use, these media representations may contribute to and reinforce negative attitudes among the public toward people with SUDs. Some evidence bears this out; an experimental study found that attitudes toward people with OUD were more positive among people randomized to read a narrative about a woman with OUD of high socioeconomic

status compared to those randomized to read about a woman with OUD of low socioeconomic status (Kennedy-Hendricks et al., 2016b).

Furthermore, high rates of stigma have been documented within key professions that interact regularly with individuals with OUD. Stigmatizing attitudes among health professionals have been shown to be widespread, which has detrimental consequences for connecting persons with OUD to treatment (Brondani et al., 2017; DeFlavio et al., 2015; Livingston et al., 2018; van Boekel et al., 2013). One recent large-scale study assessing primary care physicians' views indicated that the rates of stigma—including measures of blame for the condition and a desire for social distance from individuals with prescription OUD—were as high as or higher than stigma rates among the general public (Kennedy-Hendricks et al., 2016a). Stigmatizing attitudes toward people with OUD are also found among professionals working in the public safety and criminal justice settings, the housing sector, and the child welfare system (Rich et al., 2005; Stringer and Baker, 2018; Wittman et al., 2017).

Fewer studies have examined stigma directed specifically toward the medications to treat OUD, particularly the agonist medications methadone and buprenorphine. Stigma toward the opioid agonists appears to be grounded in the misperception that these medications are substituting one drug for another (Volkow et al., 2014). A 2017 national public opinion study revealed low rates of awareness among the public about the evidence base for medications to treat OUD; Blendon and Benson found that half of U.S. adults reported believing that there is no effective treatment for OUD (Blendon and Benson, 2018). Similarly, attitudinal surveys and qualitative data collected from professional groups indicate high levels both of misinformation and of stigma about agonist medication for OUD among personnel within drug courts (Matusow et al., 2013) and in the prison system (McKenzie et al., 2009; Nunn et al., 2009). Semi-structured interviews with individuals with OUD using methadone confirm that this group experiences high rates of stigma related to their medication use in interactions with the public and with health care professionals (Woo et al., 2017). Some limited evidence suggests that as clinicians gain experience treating patients with OUD with buprenorphine, they gain more positive perceptions about the role of medications in effective treatment (Thomas et al., 2008).

A systematic review of studies examining the consequences of the high rates of stigma experienced by individuals who use drugs found consistent evidence that stigma has a detrimental effect on their psychological well-being (Kulesza et al., 2013). In turn, shame or self-stigma is characterized as the internalization of the social opprobrium from public stigmatization that leads to the association of negative stereotypes with addiction (Matthews et al., 2017). While it makes intuitive sense that self-stigma would reduce treatment seeking (Olsen and Sharfstein, 2014), more research is needed

to better understand how self-stigma and negative attitudes toward OUD medications among people with OUD may inhibit an individual from entering treatment.

In the context of stigma, increasing attention has focused on the role of language in reinforcing negative perceptions about OUD (McGinty et al., 2017). Terms such as "substance abuser" have been shown in randomized experiments to increase stigma relative to person-centered terms like "person with a substance use disorder" (Kelly and Westerhoff, 2010). Other research studies based on randomized experiments have confirmed that the use of certain terms can reinforce blame of individuals with OUD and drive up stigma rates (Ashford et al., 2018a,b). Conversely, Ashford and colleagues found that use of the term "pharmacotherapy" produced more positive associations than the term "medication-assisted treatment" (Ashford et al., 2018b). This research has prompted stigma-reduction efforts focused on language (McGinty et al., 2017; Wakeman, 2017). Recent efforts have included the release of a memorandum on terminology from the White House Office of National Drug Control Policy (ONDCP, 2017), *Changing the Language of Addiction*, and a 2017 version of the Associated Press Stylebook recommending more careful attention to language by reporters covering news stories about the opioid epidemic (Aliferis, 2017).

It will be critical to build an evidence base for effectively confronting stigma associated with medications for OUD, particularly opioid agonists. A small but growing body of evidence is being used to identify and test the effectiveness of communications strategies targeting the general public and professionals in key sectors (e.g., health care, law enforcement, corrections) in an effort to reduce stigma and to encourage higher rates of entry into medication-based treatment. There has also been a growing interest in increasing awareness of the benefits of medication for OUD and in decreasing stigma through communications campaigns (McGinty et al., 2017). Approaches highlighting the effectiveness of medication-based treatment in helping patients sustain remission (McGinty et al., 2015) and approaches presenting sympathetic narratives (Bachhuber et al., 2015)—particularly those that illuminate the barriers that people with OUD face in trying to access treatment (Kennedy-Hendricks et al., 2016b)—have been shown to be effective in reducing stigma, but they need to be studied further.

CONCERNS ABOUT DIVERSION OF MEDICATIONS FOR OUD

Concerns about the misuse and diversion of medications for OUD also contribute to the insufficient numbers of providers willing to prescribe them. Evidence suggests that these concerns emanate from stigma and misunderstanding about the motivations for using diverted medication. A fear of patients engaging in the diversion of medication is cited by prescribers

as a barrier to treating individuals with OUD (Lin et al., 2018; Netherland et al., 2009). One national survey of buprenorphine prescribers found that one-third of respondents viewed diversion as a significant or very significant concern; half reported that they would no longer be willing to see a patient suspected of diversion (Lin et al., 2018). But education can help. A survey of both buprenorphine-waivered and non-waivered physicians found that 26 percent of non-waivered physicians were concerned about diversion, compared with 10 percent of waivered physicians (Huhn and Dunn, 2017).

Providers' concerns about the diversion of medication are inconsistent with available data, particularly in the context of medications that are formulated with deterrent properties, such as buprenorphine/naloxone. The buprenorphine/naloxone formulation was developed as a deterrent to misuse because it blocks the rewarding effects of opioids and triggers withdrawal if injected. Rates of misuse of the buprenorphine/naloxone formulation are much lower than for the mono-buprenorphine formulation. The Research Abuse, Diversion and Addiction-Related Surveillance System, which tracks the rates of misuse and diversion of medications, found that past-month injection use of mono-buprenorphine was 45 percent, compared with 16 percent for the buprenorphine/naloxone formulation (Lofwall and Walsh, 2014). Due to the higher rates of misuse of the mono-buprenorphine, the combination product is the most commonly prescribed formulation. Of the different formulations of buprenorphine/naloxone, rates of both misuse and diversion are lowest for the buprenorphine/naloxone film (Lavonas et al., 2014). Methadone diversion rates in the United States have been declining by 13 percent each year since 2011 (Jones et al., 2016) and are now slightly lower than the rates for buprenorphine. To put diversion of OUD medications in context, it is worth noting that these rates are lower than the diversion rates for other prescribed medications. For instance, prescribed antibiotics and allergy medications are diverted at rates of 25 and 21 percent, respectively (Caviness et al., 2013; Goldsworthy et al., 2008; Lofwall and Walsh, 2014).

Importantly, the rates of both misuse and diversion decline as buprenorphine availability increases (Cicero et al., 2007; Lofwall and Walsh, 2014). The reasons reported for misuse or diversion include peer pressure, a desire to help a friend or family member or to make money, and a lack of access to buprenorphine treatment (Fox et al., 2015; Lofwall and Walsh, 2014). While some individuals with OUD report misusing buprenorphine to achieve intoxication, more report using it to relieve symptoms of withdrawal (Lavonas et al., 2014).

INADEQUATE PROFESSIONAL EDUCATION AND TRAINING

Another barrier to the availability and use of medications to treat OUD is the lack of appropriate education and training among health care providers and personnel in law enforcement and the judicial system.

Health Workforce Education and Training

A broad range of professions typically provide treatment or related services for addiction in the United States, including physicians, physician assistants (PAs), nurses, and nurse practitioners (NPs); psychologists, social workers, and therapists; pharmacists; and addiction counselors. However,

> few among the broad range of providers who may treat patients with addiction are trained in or knowledgeable about evidence-based practices in addiction prevention and treatment. . . . Compounding this problem is that the diversity in education and training among the different types of individuals providing addiction treatment results in inconsistent treatment approaches and care for patients with addiction. (CASA, 2012, p. 178)

Because addiction treatment is typically separate from mainstream health systems (Frank and Glied, 2016), education about OUD is often neither required nor standardized for health care providers in the United States. The American Board of Medical Specialties only recognized addiction medicine as a subspecialty in 2015 (ABMS, 2016), and many schools and training programs have limited access to experts to develop and teach curricula. Consequently, providers often lack the education required to address numerous aspects of OUD assessment and treatment (Merrill, 2002). Even though treating addiction has similarities to treating other chronic conditions, health education curricula do not educate all providers about addiction (Merrill et al., 2002; Moran et al., 2017). Integrating addiction treatment into mainstream health systems could expand treatment capacity and improve providers' education about addiction medicine (Merrill, 2002). It should be noted, however, that the sole reliance on workforce education and training is not an assurance that evidence-based interventions will be implemented into standard care (Patterson Silver Wolf, 2015; Patterson Silver Wolf et al., 2017).

Law Enforcement and Judicial System Education and Training

For patients with OUD, critical treatment decisions often occur in the law enforcement and judicial systems rather than in medical settings. However, no policies are in place to require that the people making these decisions have received any education about evidence-based OUD treat-

ment. Education and training about OUD for court officers could increase the uptake of medications to treat OUD. Probation and parole officers also need to be trained on medications used to treat people with OUD. Many prison medical directors limit treatment to abstinence-only or detoxification-only modalities for people with OUD in their prisons. A survey of prison medical directors across the United States revealed that many were not familiar with the medical and social benefits of providing medications for OUD—particularly buprenorphine—in correctional facilities (Nunn et al., 2009). Implementing methadone treatment in correctional facilities can be logistically complicated and impeded by stigma toward the medication among management and staff; however, those challenges can and should be addressed, given the potential health and social benefits to be gained by providing the medication (McKenzie et al., 2009).

SYSTEM FRAGMENTATION

The delivery and financing of treatment for people with OUD is rarely integrated with care delivered in the broader medical care system. Separate addiction treatment delivery settings and care financing streams are reinforced by regulatory and legal requirements that impose further barriers on accessing medication-based treatment for OUD. The existence of distinct treatment systems and financing mechanisms for SUDs has created sizable barriers to providing integrated services, particularly for people who have OUD and co-occurring medical or mental health conditions. For example, while primary care settings are an important venue for providing care for most chronic medical conditions, these settings have not historically been a prominent locale for addiction treatment.

Similarly, the sources of payment for SUD treatments differ in important respects from the broader medical care system. Compared to the general medical treatment sector, a substantially larger share of the financing of SUD treatment—including OUD treatment—comes from public sources. In 2014, for example, 69 percent of SUD treatment was paid via public sources, including Medicaid (21 percent), Medicare (6 percent), other federal sources (12 percent), and other state and local sources (29 percent) (SAMHSA, 2016). Only 18 percent of financing for SUD treatment is paid via private insurance: 9 percent paid by consumers out of pocket and 4 percent paid through other private sources (SAMHSA, 2016). A lack of care integration and underfunding are legacies of the historical separation of drug treatment from the mainstream system, with what limited funding exists coming primarily from state and local funding grants rather than through insurance programs (Buck, 2011). Unlike insurance, these funding sources can lead to waitlists if funded slots are insufficient to meet treatment needs within a community.

In the United States, a large share of SUD treatment has been provided through a network of specialty addiction treatment facilities, but only 6.1 percent of these facilities offered all three FDA-approved medications in 2016 (Mojtabai et al., 2019). The share of facilities offering methadone barely changed over the past decade, from 9.4 percent of facilities offering methadone in 2007 to 10.3 percent in 2016. The reasons why some facilities offer medications and others do not is not well understood, although the rates of offering medications for OUD are higher in regions with heightened past-year heroin use and overdose death rates.

The provision of medications for OUD in treatment facilities varies substantially across the country. Among outpatient specialty SUD treatment facilities, the highest rates of offering medications for OUD are found in Rhode Island (76.1 percent), New York (73.7 percent), and Vermont (73.7 percent). The states with the lowest rates of offering medications include Idaho (16.8 percent), Arkansas (14.1 percent), and Hawaii (8.6 percent) (Mojtabai et al., 2019). Recent estimates indicate that only 23 percent of publicly funded facilities in the country offer medication-based treatment for OUD (Knudsen et al., 2010). Among those facilities, the likelihood of medication being adopted and offered was greater in programs endorsing cognitive behavioral therapy than in programs emphasizing 12-step approaches (Knudsen et al., 2010). Publicly funded programs are also less likely to have a physician on staff to prescribe medications for OUD (Abraham et al., 2013).

System fragmentation poses barriers beyond the health care sector that extend to other settings with high prevalence rates of OUD. For example, as was noted in Chapter 4, major barriers to OUD medication uptake and continuation are driven by the high rates of OUD within criminal justice settings, the lack of availability of medication-based treatment during incarceration, and the absence of strong connections with outpatient treatment in community settings offering medications upon release from incarceration (Fox et al., 2015). The implementation of comprehensive medication-based treatment programs for OUD in correctional settings has been shown to be feasible and is associated with significant mortality declines (Green et al., 2018).

To better address this fragmentation, research is needed on system integration models. For example, research could explore how office-based collaborative care approaches used to treat depression in primary care with specialty consultation, care management, and peer support might work in the context of medication-based OUD treatment. Future research could focus on patient-centered care approaches that measure the preferences of individuals with OUD, including their preferred attributes of treatment or settings for receiving treatment. For example, some research suggests a higher willingness to pay for SUD treatment in primary care settings than

in specialty addiction treatment settings (Epstein et al., 2015). In a large national sample of individuals who met the diagnostic criteria for SUD but were not currently in treatment, only 24.6 percent reported being willing to enter drug treatment in specialty settings, compared with 37.2 percent for primary care (Barry et al., 2016a). Additionally, little is known about patient preferences for integrated delivery system approaches, such as provider co-location, which allow individuals to receive addiction care alongside primary care and chronic or infectious disease management for co-occurring conditions. Furthermore, research is needed on how best to integrate care for justice-involved individuals with OUD and other health care needs who are moving into community-based treatment settings.

LEGAL AND REGULATORY BARRIERS

Legal and regulatory barriers prevent broad access to medication-based treatment for OUD within the mainstream of the medical care system. As noted previously, methadone is the most stringently regulated of the three FDA-approved medications. It can be dispensed only by opioid treatment programs (OTPs) that are certified by the Substance Abuse and Mental Health Services Administration (SAMHSA) and registered with the Drug Enforcement Administration (DEA). Buprenorphine can only be prescribed for OUD by providers after they receive training and specialized certification by the DEA. In contrast, extended-release naltrexone can be prescribed by any licensed health care provider.

Legal and Regulatory Barriers for Methadone

In providing methadone, OTPs have limited flexibility in tailoring treatment plans to the individual needs of patients. Regulations with little to no evidence base—which vary by state—often restrict take-home medication privileges, require supervised medication consumption, and mandate the frequency of urine testing and counseling. Patients receiving care through an OTP are mandated to receive counseling as part of their treatment. However, studies of the effectiveness of this counseling have not demonstrated differences in treatment retention or opioid use among patients randomized to receive little or no interaction with clinic drug counselors as compared with those who received the federally mandated level of counseling (Gruber et al., 2008; Schwartz et al., 2006, 2012; Yancovitz et al., 1991). See Chapter 2 for a more detailed discussion of behavioral interventions in conjunction with medication. Most patients receiving methadone are required to visit treatment programs daily to receive their medications. For some patients, these rigid and time-consuming requirements can impede their ability to find and maintain employment and can affect their relation-

ships; these requirements may also discourage providers from opening new treatment programs (Harris and McElrath, 2012). As a strategy to increase access to evidence-based treatment, there has been increased attention on removing regulatory barriers to prescribing methadone in primary care. Methadone may be prescribed in primary care clinics and filled in community pharmacies in Australia, Canada, and Great Britain (Merrill, 2002). Pilot studies examining the use of methadone in primary care suggest that this care delivery model is feasible and can positively affect treatment access and retention (Fiellin et al., 2001; Merrill et al., 2005). For example, a randomized controlled trial comparing office-based care versus OTP care for people who are stabilized on methadone treatment found physician offices to be a feasible and effective setting for maintenance treatment (Fiellin et al., 2001). Calls are increasing to allow methadone to be prescribed for OUD in a wider range of medical settings (Samet et al., 2018).

Legal and Regulatory Barriers for Buprenorphine and Naltrexone

Buprenorphine is less stringently regulated at the federal level than methadone, but federal regulations on certification and state regulations on the scope of practice result in limited provider capacity. The Drug Addiction Treatment Act (DATA) of 2000 allowed physicians who completed an 8-hour course to become waivered by the DEA to prescribe buprenorphine in office-based settings. Initially, federal requirements limited waivered providers to treating only 30 patients with OUD in their first year of certification and 100 thereafter. The Comprehensive Addiction and Recovery Act (CARA) of 2016[1] increased the maximum number of patients that waivered physicians could treat concurrently to 275 for physicians who met certain criteria, but the eligibility requirements may be difficult for rural physicians to meet. Federal guidelines also require providers to reduce the risk of diversion and to provide patients with reasonable access to complementary services, such as counseling (CRS, 2018). Fifty-six percent of U.S. counties now have a physician with a DEA waiver, which is an increase from 47 percent in 2012 (Andrilla et al., 2018b). CARA also allowed NPs and PAs who complete 24 hours of training to treat up to 30 patients concurrently in the first year, and 100 patients in subsequent years, for a 5-year time period. In 2018 the Substance Use–Disorder Prevention that Promotes Opioid Recovery and Treatment for Patients and Communities Act permanently allowed NPs and PAs to prescribe buprenorphine. The bill further aims to increase access to medications for OUD by allowing nurse anesthetists, nurse midwives, and clinical nurse specialists to prescribe

[1] Public Law 114-198.

buprenorphine for the next 5 years.[2] Twenty-eight states prohibit NPs from prescribing buprenorphine without oversight by a waivered M.D. Three states (Oklahoma, Tennessee, and Wyoming) prohibit any prescribing of buprenorphine by NPs, and Kentucky prohibits prescribing by PAs.

The inclusion of NPs and PAs in the workforce that can prescribe medication-based treatment has modestly increased the provider supply across the country. Among urban counties, 45.9 percent have a waivered NP and 24.5 percent have a waivered PA. Among rural counties, 13.8 percent have a waivered NP and 4.6 percent have a waivered PA (Andrilla et al., 2018b). The increase in the number of waivered providers is also reflected in the changes in the provider-to-population ratios since 2012. In urban counties, the number of waivered physicians per 100,000 population increased from 6.3 to 11.0; furthermore, adding NPs and PAs to this provider workforce raised the current urban provider-to-population ratio to 12.4 (Andrilla et al., 2018a,b).

Despite this progress, most providers who are waivered to prescribe buprenorphine maintain patient panels well below the regulated patient limits. According to one estimate, fewer than 30 percent of buprenorphine-waivered physicians were actually prescribing the medication, and less than 50 percent of waivered physicians had elected to be listed on SAMHSA's physician and treatment locator site (Moran et al., 2017). Most waivered providers treat a small number of patients: half of providers treat five or fewer patients with buprenorphine and one-third treat just a single patient (Moran et al., 2017). Even if all waivered providers were prescribing at capacity, the treatment coverage would still be inadequate to meet the need for treatment for OUD. Estimates suggest that just half of all people with OUD would receive treatment if all waivered providers were prescribing at capacity (Huhn and Dunn, 2017; Jones et al., 2015; Murphy et al., 2014; Rosenblatt et al., 2015).

Reasons cited by waivered physicians for not prescribing buprenorphine at capacity include a lack of time for new patients, concern about diversion, and reimbursement concerns (Huhn and Dunn, 2017; Molfenter et al., 2015). Another survey reported that diversion concerns were common, especially among rural physicians (Andrilla et al., 2017). Waivered physicians tend to have partners who are also waivered (Hutchinson et al., 2014). Additional barriers to buprenorphine prescription reported by waivered primary care physicians include a lack of institutional support, mental health support, and psychosocial support (Hutchinson et al., 2014). Waivered providers have also reported that the DEA's approach can be "threatening," and some buprenorphine-waivered providers feel that they

[2] See House amendment to Senate amendment to House of Representatives bill H.R. 6. https://www.congress.gov/115/bills/hr6/BILLS-115hr6eah.pdf (accessed February 12, 2019).

are unfairly scrutinized by the DEA (Moran et al., 2017). More recent aggressive enforcement strategies by the DEA and several state attorneys general—including increases in raiding, auditing, and launching criminal investigations of waivered providers—perpetuate the fear of such surveillance that has been articulated by waivered and non-waivered providers (Mendoza et al., 2016).

When asked about their willingness to prescribe buprenorphine, non-waivered providers report that they are concerned about attracting people who use drugs to their practices as well as about encountering resistance from clinical practice partners (Andrilla et al., 2017). Other reasons for not prescribing cited by non-waivered providers include concerns about managing the volume of patient requests for buprenorphine and concerns about buprenorphine diversion (Huhn and Dunn, 2017). In a survey of non-waivered providers, respondents indicated a number of factors that could increase their willingness to begin prescribing buprenorphine, including being provided with information about local counseling resources, having access to an experienced prescriber for consultation, and receiving continuing medical education about OUD (Huhn and Dunn, 2017). In another survey of family physicians, the barriers to adopting buprenorphine treatment included the lack of adequately trained office staff, a lack of time, inadequate office space, regulatory requirements, a mistrust of people with addiction, the perception of people with addiction as a difficult population, and poor perceived efficacy of buprenorphine treatment (DeFlavio et al., 2015).

In contrast to the literature examining why providers do or do not obtain and use the DATA waiver to treat OUD, no evidence base supports the waiver process itself. Buprenorphine management is less risky and complicated than many other treatments that do not require special certification (Wakeman and Barnett, 2018). To expand access to buprenorphine treatment, there have been calls to eliminate prescribing limits on the grounds that there is no evidence base for limiting access to this medication (Fiscella et al., 2018). Another concern that has been raised involves the need to develop best practices to enhance the certification processes for prescribing clinicians and to better ensure high-quality prescribing practices (Blum et al., 2016).

Relative to methadone and buprenorphine, the legal barriers to accessing naltrexone are low. Naltrexone can be provided in an office setting with few regulatory requirements. The most common barrier to wider access identified by providers of naltrexone is related to its high cost, about $1,200 per monthly dose (Alanis-Hirsch et al., 2016).

Privacy Regulations

Privacy regulations, particularly 42 Code of Federal Regulations (CFR) part 2 regulations, present a gap in knowledge in terms of policy impact on individual behavior, as it is unclear whether they act to promote or discourage treatment initiation and retention. The 42 CFR part 2 regulations stipulate that a program that receives any federal funding—including funding through the Medicaid or Medicare programs—and "holds itself out as providing . . . treatment" of SUDs may not disclose that its patients have a SUD or are in treatment without explicit patient consent or a court order (SAMHSA, 2018). Given the history of stigma and discrimination, this regulation protects the privacy of patients with SUDs, similar to statutes protecting sensitive health conditions like HIV. The regulation creates a high bar for disclosure of treatment status to individuals or organizations, which have the power to sanction patients for engaging in evidence-based medical treatment, such as the criminal justice system, governmental agencies such as Child Protective Services, and housing corporations. In this way, privacy protections may encourage patients to seek treatment at specialized centers. At the same time, the special privacy protection contributes to the traditional separation of addiction treatment from the rest of medical care. Consequently, a patient's primary care, inpatient, mental health, and SUD treatment provider may not be aware of the patient's status in treatment for OUD, unless the patient chooses to disclose that status; this can complicate the patient's overall medical treatment regimen and discourage continuity of treatment for OUD when a patient transitions from one care location to another.

Another knowledge gap concerns differences in medical and pharmacy records and how this impacts patient treatment selection. Extended-release naltrexone is generally covered under a medical benefit and administered in a provider's office, so the level of privacy depends on whether the provider is subject to 42 CFR part 2. On the other hand, state and regional Prescription Drug Monitoring Programs (PDMPs) track records of controlled substances, so the vast majority of patients who are maintained on buprenorphine have their treatment status disclosed without their consent—whether or not their provider's medical record is subject to the 42 CFR part 2 regulations. Because methadone for OUD is provided only at licensed specialty programs, 42 CFR part 2 regulations prohibit disclosure of dispensed medication to the PDMP.

PUBLIC AND PRIVATE INSURANCE BARRIERS

Regulations that govern public and private insurance coverage pose substantial barriers to patients' ability to access medication-based treatment

for OUD. Adjusting policies related to coverage and reimbursement has the potential to expand access to life-saving medications across the country and to make headway against the opioid epidemic.

Medicaid

Medicaid is the single most important source of insurance coverage for individuals with OUD. It is the largest health insurance program in the United States, covering more than 62 million Americans, including millions of the nation's lowest-income individuals and families. Medicaid covers an estimated 4 in 10 non-elderly adults with OUD (Zur and Tolbert, 2018), and more than $9 billion was paid by Medicaid for the treatment of OUD in 2016 alone (Niederee and Lawless, 2018). Research suggests that Medicaid coverage can help individuals access medication-based treatment for OUD and facilitate treatment retention. States that expanded access to Medicaid under the Patient Protection and Affordable Care Act (ACA) have experienced increased use of buprenorphine treatment (Saloner et al., 2018; Sharp et al., 2018; Wen et al., 2017). One analysis found that Medicaid expansion states were associated with a 70 percent increase in buprenorphine prescriptions covered by Medicaid and a 50 percent increase in buprenorphine spending (Wen et al., 2017). Having stable Medicaid eligibility is also associated with higher rates of retention on medication for OUD (Deck et al., 2009). One study found a 50 percent lower risk of return to use among Medicaid enrollees treated with medication relative to other treatments, and longer treatment duration among Medicaid enrollees was associated with lower return to use rates (Clark et al., 2011). Among publicly funded addiction treatment organizations, reliance on Medicaid reimbursement has been positively associated with offering medications for OUD (Knudsen et al., 2010). Under one state's Medicaid program, enrollees treated with OUD medication had lower overall health care expenditures; coupled with reduced medical care costs, this offset the cost of medication-based treatment for OUD (Mohlman et al., 2016). Conversely, the elimination of Medicaid coverage for active methadone patients under one state's Medicaid program led to negative outcomes for patients with OUD, including an increased inability to afford treatment, increased property crimes, greater frequency of medical care visits, and employment-related challenges (Fuller et al., 2006).

Important gaps remain in Medicaid coverage for medications to treat OUD. One survey identified five states that excluded both buprenorphine and methadone from their Medicaid coverage policies (Burns et al., 2016); 14 states lack any facility that offers medication-based treatment and also accepts Medicaid coverage for OUD (Jones et al., 2018). Use management policies under Medicaid serve as additional barriers to medication

access, including prior-authorization requirements, formulary restrictions, and restrictions on treatment duration and doses (Moran et al., 2017). In addition, new approaches being instituted in some state Medicaid programs through section 1115 waivers including work requirements, increased cost-sharing and deductibles, and other consumer-oriented approaches such as health savings accounts that put enrollee coverage at risk for failure to make payments could pose barriers to access and continuation on medication for OUD (Somers et al., 2018).

Medicaid and Incarceration

Importantly, Medicaid expansion under the ACA has created unprecedented opportunities for addressing the low rates of insurance coverage among individuals with OUD who are returning to the community following incarceration. Medicaid expansion meaningfully affects justice-involved individuals, which is a group that consists disproportionally of low-income men who have historically been excluded from Medicaid coverage (Cuellar and Cheema, 2012). Birnbaum and colleagues report that nearly all criminal justice–involved individuals are eligible for Medicaid in expansion states upon release (Birnbaum et al., 2014). By federal regulation, however, Medicaid dollars cannot be used to cover health care provided while a person is incarcerated (Somers et al., 2014). Medicaid coverage must be terminated or suspended during periods of incarceration (Gates et al., 2014; Rosen et al., 2014). Typically, people on medication-based treatment for OUD who become incarcerated are rapidly tapered off medication, and people with OUD are rarely initiated on medication-based treatment while incarcerated. For people who are discontinued when incarcerated, being disconnected from care contributes to lost opportunities to more cost-effectively and humanely treat chronic diseases; it also perpetuates extremely high overdose mortality risk upon release. For an inmate leaving incarceration in states that terminate Medicaid benefits, re-enrolling in coverage can cause months-long delays that contribute to disruptions in the receipt of care. Such disruption has negative clinical impacts for patients with OUD. Some states are instituting policies to lower the barriers to Medicaid coverage for justice-involved individuals, including those with OUD (Bandara et al., 2015). Those policies include suspending rather than terminating Medicaid benefits during incarceration, allowing enrollment in Medicaid during incarceration, and presumptive eligibility policy options.

Private Insurance

Private insurance also offers important opportunities for expanding access to medications for OUD. Evidence suggests an association between

gaining private health insurance and accessing medication-based treatment for OUD. One study of individuals injecting drugs found that when participants acquired private insurance, the likelihood that they would report a buprenorphine prescription and a regular source of medical care increased (Feder et al., 2018). However, until recently, private coverage for SUD treatment required higher cost sharing and special annual service caps relative to the insurance benefits for other medical conditions (Barry and Sindelar, 2007; Gabel et al., 2007).

A number of recent policy changes have lowered barriers to receiving medication-based treatment for OUD paid for via insurance. The Mental Health Parity Act of 1996 (MHPA) mandated that large-group health plans cannot impose annual or lifetime dollar limits on mental health benefits that are less favorable than any such limits imposed on medical and surgical benefits. The Mental Health Parity and Addiction Equity Act of 2008 preserves the MHPA protections and adds significant new protections, such as extending the parity requirements to SUDs. Evidence suggests that as a result of this law, the treatment rate for SUDs increased by 9 percent in all specialty treatment facilities and by 15 percent in facilities accepting private insurance (Wen et al., 2013). Federal parity also increased inpatient SUD admissions. Some evidence also suggests that the parity ensured by this law led to a decrease in the financial burden on families of paying for addiction treatment via commercial insurance (Azzone et al., 2011). Importantly, parity requirements and other insurance market changes extend private health insurance to more individuals with OUD. These include the "dependent care" provision, which allows children to be kept on their parents' insurance until the age of 26 years, as well as the ACA ban of the once common insurance industry practice of refusing to sell insurance policies to individuals with pre-existing disorders (Barry et al., 2016b; Humphreys and Frank, 2014).

Nonetheless, barriers continue to prevent access to medication for OUD under private insurance. For example, a recent study of benefits in 2017 marketplace plans found that 14 percent of health plans did not cover any formulations of buprenorphine/naloxone. Despite the new patient protections, plans were more likely to require prior authorization for covered office-based buprenorphine or naltrexone treatment than for short-acting opioid pain medications. Only 10.6 percent of plans covered implantable buprenorphine, while 26.1 percent covered injectable naltrexone (Huskamp et al., 2018).

Reimbursement and Payment System Barriers

Research indicates that altering reimbursement and payment incentives could lower the barriers to accessing medications for OUD. Reimbursement

concerns—some of which are specific to Medicaid (Quest et al., 2012)—are a commonly cited barrier to buprenorphine prescribing, particularly among waivered physicians (Barry et al., 2009). The predominant fee-for-service model of reimbursement for providers rewards quantity rather than care quality (Fodeman, 2017). Efforts are under way to address this by shifting to value-based payment systems through accountable care and payment reforms (e.g., global payment, bundled payment). Payment changes that drive health systems to provide high-value care could be instrumental in increasing OUD medication-based treatment rates. However, some evidence suggests that the addiction treatment sector is not keeping pace with the rest of the health care field in adopting new value-based payment systems (McDowell et al., 2018; Stuart et al., 2017).

A 2006 Institute of Medicine report made sweeping recommendations to improve the quality of SUD care in the United States, but few of those recommendations have been implemented (IOM, 2006). The lack of performance metrics for measuring the uptake of OUD medication poses additional barriers to progress (Thomas et al., 2011). An important area in which SUD care is lagging behind the rest of the medical care sector is the development, evaluation, and implementation of health quality measures aimed at increasing patients' access to medications and their continuation in evidence-based treatment for OUD; these measures include metrics that can be used in value-based payment systems (Pincus et al., 2016). For example, a performance metric for OUD medication could track and reward providers who are able to maintain a sizable share of their patient populations in longer-term, medication-based treatment. Other types of payment incentives might also be considered—for example, requiring that substance use treatment facilities receiving federal block grant funding provide medications for OUD as a condition of participation.

Conclusion 7: Confronting the major barriers to the use of medications to treat opioid use disorder is critical to addressing the opioid crisis.

The major barriers to the use of medications for OUD include

- High levels of misunderstanding and stigma toward drug addiction, individuals with OUD, and the medications to treat it.
- Inadequate education of the professionals responsible for working with people with OUD, including treatment providers and law enforcement and other criminal justice personnel.
- Current regulations around methadone and buprenorphine, such as waiver policies, patient limits, restrictions on settings where medications are available, and other policies that are not supported by evidence or employed for other medical disorders.
- The fragmented system of care for people with OUD and current financing and payment policies.

REFERENCES

ABMS (American Board of Medical Specialties). 2016. *ABMS officially recognizes addiction medicine as a subspecialty*. Press Release on March 14, 2016. https://www.abms.org/news-events/abms-officially-recognizes-addiction-medicine-as-a-subspecialty (accessed Feburary 28, 2019).

Abraham, A. J., H. K. Knudsen, T. Rieckmann, and P. M. Roman. 2013. Disparities in access to physicians and medications for the treatment of substance use disorders between publicly and privately funded treatment programs in the United States. *Journal of Studies on Alcohol and Drugs* 74(2):258–265.

Alanis-Hirsch, K., R. Croff, J. H. Ford, K. Johnson, M. Chalk, L. Schmidt, and D. McCarty. 2016. Extended-release naltrexone: A qualitative analysis of barriers to routine use. *Journal of Substance Abuse Treatment* 62:68–73.

Alexander, L., and B. G. Link. 2003. The impact of contact on stigmatizing attitudes toward people with mental illness. *Journal of Mental Health* 12(3):271–289.

Aliferis, L. 2017. In stylebook, AP directs its reporters: Addiction is a disease. *California Health Care Foundation*, June 13. https://www.chcf.org/blog/in-stylebook-ap-directs-its-reporters-addiction-is-a-disease (accessed February 12, 2019).

Andrilla, C. H. A., C. Coulthard, and E. H. Larson. 2017. Barriers rural physicians face prescribing buprenorphine for opioid use disorder. *Annals of Family Medicine* 15(4):359–362.

Andrilla, C. H. A., C. Coulthard, and D. G. Patterson. 2018a. Prescribing practices of rural physicians waivered to prescribe buprenorphine. *American Journal of Preventive Medicine* 54(6S3):208–214.

Andrilla, C. H. A., T. E. Moore, D. G. Patterson, and E. H. Larson. 2018b. Geographic distribution of providers with a DEA waiver to prescribe buprenorphine for the treatment of opioid use disrder: A 5-year update. *Journal of Rural Health* 35(1):108–112.

Ashford, R. D., A. M. Brown, and B. Curtis. 2018a. The language of substance use and recovery: Novel use of the go/no-go association task to measure implicit bias. *Health Communication* June 4:1–7.

Ashford, R. D., A. M. Brown, and B. Curtis. 2018b. Substance use, recovery, and linguistics: The impact of word choice on explicit and implicit bias. *Drug and Alcohol Dependence* 189:131–138.

Azzone, V., R. G. Frank, S. L. Normand, and M. A. Burnam. 2011. Effect of insurance parity on substance abuse treatment. *Psychiatric Services* 62(2):129–134.

Bachhuber, M. A., E. E. McGinty, A. Kennedy-Hendricks, J. Niederdeppe, and C. L. Barry. 2015. Messaging to increase public support for naloxone distribution policies in the United States: Results from a randomized survey experiment. *PLOS ONE* 10(7):e0130050.

Bandara, S. N., H. A. Huskamp, L. E. Riedel, E. E. McGinty, D. Webster, R.E. Toone, and C. L. Barry. 2015. Leveraging the Affordable Care Act to enroll justice-involved populations in Medicaid: State and local efforts. *Health Affairs (Millwood)* 34(12):2044–2051.

Barry, C. L., and J. L. Sindelar. 2007. Equity in private insurance coverage for substance abuse: A perspective on parity. *Health Affairs (Millwood)* 26(6):w706–w716.

Barry, C. L., E. E. McGinty, B. A. Pescosolido, and H. H. Goldman. 2014. Stigma, discrimination, treatment effectiveness, and policy: Public views about drug addiction and mental illness. *Psychiatric Services* 65(10):1269–1272.

Barry, C. L., A. J. Epstein, D. A. Fiellin, L. Fraenkel, and S. H. Busch. 2016a. Estimating demand for primary care-based treatment for substance and alcohol use disorders. *Addiction* 111(8):1376–1384.

Barry, C. L., H. H. Goldman, and H. A. Huskamp. 2016b. Federal parity in the evolving mental health and addiction care landscape. *Health Affairs (Millwood)* 35(6):1009–1016.

Barry, D. T., K. S. Irwin, E. S. Jones, W. C. Becker, J. M. Tetrault, L. E. Sullivan, H. Hansen, P. G. O'Connor, R. S. Schottenfeld, and D. A. Fiellin. 2009. Integrating buprenorphine treatment into office-based practice: A qualitative study. *Journal of General Internal Medicine* 24(2):218–225.

Birnbaum, N., M. Lavoie, N. Redmond, C. Wildeman, and E. A. Wang. 2014. Termination of Medicaid policies and implications for the Affordable Care Act. *American Journal of Public Health* 104(8):e3–e4.

Blanco, C., M. Iza, R. P. Schwartz, C. Rafful, S. Wang, and M. J. D. Olfson. 2013. Probability and predictors of treatment-seeking for prescription opioid use disorders: A national study. *Drug and Alcohol Dependence* 131(1–2):143–148.

Blendon, R. J., and J. M. Benson. 2018. The public and the opioid-abuse epidemic. *New England Journal of Medicine* 378(5):407–411.

Blum, K., M. Gold, H. W. Clark, K. Dushaj, and R. D. Badgaiyan. 2016. Should the United States government repeal restrictions on buprenorphine/naloxone treatment? *Substance Use & Misuse* 51(12):1674–1679.

Brondani, M. A., R. Alan, and L. Donnelly. 2017. Stigma of addiction and mental illness in healthcare: The case of patients' experiences in dental settings. *PLOS ONE* 12(5): e0177388.

Buck, J. A. 2011. *The looming expansion and transformation of public substance abuse treatment under the Affordable Care Act*. Health Affairs. https://www.healthaffairs.org/doi/10.1377/hlthaff.2011.0480 (accessed February 20, 2019).

Bullock, H. E., K. F. Wyche, and W. R. Williams. 2001. Media images of the poor. *Journal of Social Issues* 57:229–246.

Burns, R. M., R. L. Pacula, S. Bauhoff, A. J. Gordon, H. Hendrikson, D. L. Leslie, and B. D. Stein. 2016. Policies related to opioid agonist therapy for opioid use disorders: The evolution of state policies from 2004–2013. *Substance Abuse* 37(1):63–69.

Capitanio, J. P., and G. M. Herek. 1999. AIDS-related stigma and attitudes toward injecting drug users among black and white Americans. *American Behavioral Scientist* 42(7):1148–1161.

CASA (Center on Addiction and Substance Abuse at Columbia University). 2012. *Addiction medicine: Closing the gap between science and practice*. New York. https://ia800406.us.archive.org/10/items/781862-casa-columbia-addiction-med/781862-casa-columbia-addiction-med.pdf (accessed Februrary 28, 2019).

Caviness, C. M., B. J. Anderson, M. A. de Dios, M. Kurth, and M. Stein. 2013. Prescription medication exchange patterns among methadone maintenance patients. *Drug and Alcohol Dependence* 127(1–3):232–238.

Cicero, T. J., H. L. Surratt, and J. Inciardi. 2007. Use and misuse of buprenorphine in the management of opioid addiction. *Journal of Opioid Management* 3(6):302–308.

Clark, R. E., M. Samnaliev, J. D. Baxter, and G. Y. Leung. 2011. The evidence doesn't justify steps by state medicaid programs to restrict opioid addiction treatment with buprenorphine. *Health Affairs* 30(8):1425–1433.

Corrigan, P. W., S. B. Morris, P. J. Michaels, J. D. Rafacz, and N. Rusch. 2012. Challenging the public stigma of mental illness: A meta-analysis of outcome studies. *Psychiatric Services* 63(10):963–973.

Couture, S. M., and D. L. Penn. 2003. Interpersonal contact and the stigma of mental illness: A review of the literature. *Journal of Mental Health* 12(3):291–305.

CRS (Congressional Research Service). 2018. *Buprenorphine and the opioid crisis: A primer for Congress*. https://fas.org/sgp/crs/misc/R45279.pdf (accessed February 12, 2019).

Cuellar, A. E., and J. Cheema. 2012. As roughly 700,000 prisoners are released annually, about half will gain health coverage and care under federal laws. *Health Affairs (Millwood)* 31(5):931–938.

Deck, D., W. Wiitala, B. McFarland, K. Campbell, J. Mullooly, A. Krupski, and D. McCarty. 2009. Medicaid coverage, methadone maintenance, and felony arrests: Outcomes of opiate treatment in two states. *Journal of Addictive Diseases* 28(2):89–102.

DeFlavio, J. R., S. A. Rolin, B. R. Nordstrom, and L. A. Kazal, Jr. 2015. Analysis of barriers to adoption of buprenorphine maintenance therapy by family physicians. *Rural and Remote Health* 15:3019.

Epstein, A. J., C. L. Barry, D. A. Fiellin, and S. H. Busch. 2015. Consumers' valuation of primary care-based treatment options for mental and substance use disorders. *Psychiatric Services* 66(8):772–774.

Feder, K. A., Krawczyk, R. Mojtabai, R. M. Crum, G. Kirk, and S. H. Mehta. 2018. Health insurance coverage is associated with access to substance use treatment among individuals with injection drug use: Evidence from a 12-year prospective study. *Journal of Substance Abuse Treatment* 96:75–81.

Fiellin, D. A., P. G. O'Connor, M. Chawarski, J. P. Pakes, M. V. Pantalon, and R. S. Schottenfeld. 2001. Methadone maintenance in primary care: A randomized controlled trial. *JAMA* 286(14):1724–1731.

Fiscella, K., S. E. Wakeman, and L. Beletsky. 2018. Buprenorphine deregulation and mainstreaming treatment for opioid use disorder. *JAMA Psychiatry*, December 26 [Epub ahead of print].

Fodeman, J. D. 2017. The opioid epidemic and the role of reimbursement. *Healthcare Transformation* 2(1). March 1. https://www.liebertpub.com/doi/full/10.1089/heat.2017.29036.jdf (accessed February 12, 2019).

Fox, A. D., J. Maradiaga, L. Weiss, J. Sanchez, J. L. Starrels, and C. O. Cunningham. 2015. Release from incarceration, relapse to opioid use, and the potential for buprenorphine maintenance treatment: A qualitative study of the perceptions of former inmates with opioid use disorder. *Addiction Science & Clinical Practice* 10(1):2.

Frank, G., and A. Glied. 2006. *Better but not well: Mental health policy in the United States since 1950*. Baltimore, MD: Johns Hopkins University Press.

Fuller, B. E., T. R. Rieckmann, D. J. McCarty, R. Ringor-Carty, and S. Kennard. 2006. Elimination of methadone benefits in the Oregon health plans and its effects on patients. *Psychiatric Services* 57(5):686–691.

Gabel, J. R., H. Whitmore, J. D. Pickreign, K. R. Levit, R. M. Coffey, and R. Vandivort-Warren. 2007. Substance abuse benefits: Still limited after all these years. *Health Affairs (Millwood)* 26(4):w474–w482.

Gates, A., S. Artiga, and R. Rudowitz. 2014. *Health coverage and care for the adult criminal justice-involved population*. Kaiser Family Foundation. September 5. https://www.kff.org/uninsured/issue-brief/health-coverage-and-care-for-the-adult-criminal-justice-involved-population (accessed February 12, 2019).

Goldsworthy, R. C., N. C. Schwartz, and C. B. Mayhorn. 2008. Beyond abuse and exposure: framing the impact of prescription-medication sharing. *American Journal of Public Health* 98(6):1115–1121.

Green, T. C., J. Clarke, L. Brinkley-Rubinstein, B. D. L. Marshall, N. Alexander-Scott, R. Boss, and J. D. Rich. 2018. Postincarceration fatal overdoses after implementing medications for addiction treatment in a statewide correctional system. *JAMA Psychiatry* 75(4):405–407.

Gruber, V. A., K. L. Delucchi, A. Kielstein, and S. L. Batki. 2008. A randomized trial of 6-month methadone maintenance with standard or minimal counseling versus 21-day methadone detoxification. *Drug and Alcohol Dependence* 94(1–3):199–206.

Harris, J., and K. McElrath. 2012. Methadone as social control: Institutionalized stigma and the prospect of recovery. *Qualitative Health Research* 22(6):810–824.

Huhn, A. S., and K. E. Dunn. 2017. Why aren't physicians prescribing more buprenorphine? *Journal of Substance Abuse Treatment* 78:1–7.

Humphreys, K., and R. G. Frank. 2014. The Affordable Care Act will revolutionize care for substance use disorders in the United States. *Addiction* 109(12):1957–1958.

Huskamp, H. A., L. E. Riedel, C. L. Barry, and A. B. Busch. 2018. Coverage of medication that treat opioid use disorder and opioids for pain management in marketplace plans, 2017. *Medical Care* 56(6):505–509.

Hutchinson, E., M. Catlin, C. H. A. Andrilla, L.-M. Baldwin, and R. A. Rosenblatt. 2014. Barriers to primary care physicians prescribing buprenorphine. *Annals of Family Medicine* 12(2):128–133.

IOM (Institute of Medicine). 2006. *Improving the quality of health care for mental and substance-use conditions*. Washington, DC: The National Academies Press.

Jones, A., B. Honermann, A. Sharp, and G. Millett. 2018. *Where multiple modes of medication-assisted treatment are available*. Health Affairs blog, January 9. https://www.healthaffairs.org/do/10.1377/hblog20180104.835958/full (accessed February 12, 2019).

Jones, C. M., and E. F. McCance-Katz. 2019. Co-occurring substance use and mental disorders among adults with opioid use disorder. *Drug and Alcohol Depend*ence 197(1):78–82. doi: 10.1016/j.drugalcdep.2018.12.030.

Jones, C. M., M. Campopiano, G. Baldwin, and E. McCance-Katz. 2015. National and state treatment need and capacity for opioid agonist medication-assisted treatment. *American Journal of Public Health* 105(8):e55–e63.

Jones, C. M., G. T. Baldwin, T. Manocchio, J. O. White, and K. A. Mack. 2016. *Trends in methadone distribution for pain treatment, methadone diversion, and overdose deaths—United States, 2002–2014*. U.S. Centers for Disease Control and Prevention. https://www.cdc.gov/mmwr/volumes/65/wr/mm6526a2.htm (accessed February 12, 2019).

Kelly, J. F., and C. M. Westerhoff. 2010. Does it matter how we refer to individuals with substance-related conditions? A randomized study of two commonly used terms. *International Journal of Drug Policy* 21(3):202–207.

Kennedy-Hendricks, A., S. H. Busch, E. E. McGinty, M. A. Bachhuber, J. Niederdeppe, S. E. Gollust, D. W. Webster, D. A. Fiellin, and C. L. Barry. 2016a. Primary care physicians' perspectives on the prescription opioid epidemic. *Drug and Alcohol Dependence* 165:61–70.

Kennedy-Hendricks, A., E. E. McGinty, and C. L. Barry. 2016b. Effects of competing narratives on public perceptions of opioid pain reliever addiction during pregnancy. *Journal of Health Politics, Policy, and Law* 41(5):873–916.

Kennedy-Hendricks, A., C. L. Barry, S. E. Gollust, M. E. Ensminger, M. S. Chisolm, and E. E. McGinty. 2017. Social stigma toward persons with prescription opioid use disorder: Associations with public support for punitive and public health-oriented policies. *Psychiatric Services* 68(5):462–469.

Knudsen, H. K., P. M. Roman, and C. B. Oser. 2010. Facilitating factors and barriers to the use of medications in publicly funded addiction treatment organizations. *Journal of Addiction Medicine* 4(2):99–107.

Kulesza, M., M. E. Larimer, and D. Rao. 2013. Substance use related stigma: What we know and the way forward. *Journal of Addictive Behaviors, Therapy, & Rehabilitation* 2(2):782.

Lavonas, E. J., S. G. Severtson, E. M. Martinez, B. Bucher-Bartelson, M. C. Le Lait, J. L. Green, L. E. Murrelle, T. J. Cicero, S. P. Kurtz, A. Rosenblum, H. L. Surratt, and R. C. Dart. 2014. Abuse and diversion of buprenorphine sublingual tablets and film. *Journal of Substance Abuse Treatment* 47(1):27–34.

Lin, L. A., M. R. Lofwall, S. L. Walsh, A. J. Gordon, and H. K. Knudsen. 2018. Perceptions and practices addressing diversion among U.S. buprenorphine prescribers. *Drug and Alcohol Dependence* 186:147–153.

Link, B. G., and J. C. Phelan. 2001. Conceptualizing stigma. *Annual Review of Sociology* 27:363–385.

Livingston, J. D., E. Adams, M. Jordan, Z. MacMillan, and R. Hering. 2018. Primary care physicians' views about prescribing methadone to treat opioid use disorder. *Substance Use & Misuse* 53(2):344–353.

Lofwall, M. R., and S. L. Walsh. 2014. A review of buprenorphine diversion and misuse: The current evidence base and experiences from around the world. *Journal of Addiction Medicine* 8(5):315–326.

Matthews, S., R. Dwyer, and A. Snoek. 2017. Stigma and self-stigma in addiction. *Journal of Bioethical Inquiry* 14(2):275–286.

Matusow, H., S. L. Dickman, J. D. Rich, C. Fong, D. M. Dumont, C. Hardin, D. Marlowe, and A. Rosenblum. 2013. Medication assisted treatment in us drug courts: Results from a nationwide survey of availability, barriers, and attitudes. *Journal of Substance Abuse Treatment* 44(5):473–480.

McDowell, M. J., A. B. Busch, A. P. Sen, E. A. Stuart, L. Riedel, C. L. Barry, and H. A. Huskamp. 2018. Participation in accountable care organizations among hospitals offering substance use disorder and mental health services. *Psychiatric Services*. https://ps.psychiatryonline.org/doi/abs/10.1176/appi.ps.201800248?rfr_dat=cr_pub%3Dpubmed&url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org&journalCode=ps (accessed February 18, 2019).

McGinty, E. E., H. H. Goldman, B. Pescosolido, and C. L. Barry. 2015. Portraying mental illness and drug addiction as treatable health conditions: Effects of a randomized experiment on stigma and discrimination. *Social Science & Medicine* 126:73–85.

McGinty, E., B. Pescosolido, A. Kennedy-Hendricks, and C. L. Barry. 2017. Communication strategies to counter stigma and improve mental illness and substance use disorder policy. *Psychiatric Services* 69(2):136–146.

McKenzie, M., A. Nunn, N. D. Zaller, A. R. Bazazi, and J. D. Rich. 2009. Overcoming obstacles to implementing methadone maintenance therapy for prisoners: Implications for policy and practice. *Journal of Opioid Management* 5(4):219–227.

McSween, J. L. 2002. The role of group interest, identity, and stigma in determining mental health policy preferences. *Journal of Health Politics, Policy, and Law* 27(5):773–800.

Mendoza, S., A. S. Rivera-Cabrero, and H. Hansen. 2016. Shifting blame: Buprenorphine prescribers, addiction treatment, and prescription monitoring in middle-class America. *Transcult Psychiatry* 53(4):465–487.

Merrill, J. O. 2002. Policy progress for physician treatment of opiate addiction. *Journal of General Internal Medicine* 17(5):361–368.

Merrill, J. O., L. A. Rhodes, R. A. Deyo, G. A. Marlatt, and K. A. Bradley. 2002. Mutual mistrust in the medical care of drug users: The keys to the "narc" cabinet. *Journal of General Internal Medicine* 17(5):327–333.

Merrill, J. O., T. R. Jackson, B. A. Schulman, A. J. Saxon, A. Awan, S. Kapitan, M. Carney, L. C. Brumback, and D. Donovan. 2005. Methadone medical maintenance in primary care: An implementation evaluation. *Journal of General Internal Medicine* 20(4):344–349.

Minior, T., S. Galea, J. Stuber, J. Ahern, and D. Ompad. 2003. Racial differences in discrimination experiences and responses among minority substance users. *Ethnicity & Disease* 13(4):521–527.

Mohlman, M. K., B. Tanzman, K. Finison, M. Pinette, and C. Jones. 2016. Impact of medication-assisted treatment for opioid addiction on medicaid expenditures and health services utilization rates in Vermont. *Journal of Substance Abuse Treatment* 67:9–14.

Mojtabai, R., C. Mauro, M. M. Wall, C. L. Barry, and M. Olfson. 2019. Medication treatment for opioid use disorders in substance use treatment facilities. *Health Affairs* 38(1):14–23.

Molfenter, T., C. Sherbeck, M. Zehner, A. Quanbeck, D. McCarty, J. S. Kim, and S. Starr. 2015. Implementing buprenorphine in addiction treatment: Payer and provider perspectives in Ohio. *Substance Abuse Treatment, Prevention, and Policy* 10:13.

Moran, G. E., C. M. Snyder, R. F. Noftsinger, and J. K. Noda. 2017. *Implementing medication-assisted treatment for opioid use disorder in rural primary care: Environmental scan.* Rockville, MD: Agency for Healthcare Research and Quality.

Morone, J. A. 1997. Enemies of the people: The moral dimension to public health. *Journal of Health Politics, Policy, and Law* 22(4):993–1020.

Murphy, S. M., P. A. Fishman, S. McPherson, D. G. Dyck, and J. R. Roll. 2014. Determinants of buprenorphine treatment for opioid dependence. *Journal of Substance Abuse Treatment* 46(3):315–319.

Netherland, J., and H. B. Hansen. 2016. The war on drugs that wasn't: Wasted whiteness, "dirty doctors," and race in media coverage of prescription opioid misuse. *Culture, Medicine, and Psychiatry* 40(4):664–686.

Netherland, J., M. Botsko, J. E. Egan, A. Saxon, C. Cunningham, R. Finkelstein, M. Gourevitch, J. A. Renner, L. Weiss, and D. Fiellin. 2009. Factors affecting willingness to provide buprenorphine treatment. *Journal of Substance Abuse Treatment* 36(3):244–251.

Niederee, K., and J. Lawless. 2018. *Hatch, Wyden seek feedback to improve Medicare, Medicaid responses to opioid epidemic*. U.S. Senate Committee on Finance. https://www.finance.senate.gov/chairmans-news/hatch-wyden-seek-feedback-to-improve-medicare-medicaid-responses-to-opioid-epidemic (accessed February 12, 2019).

Nunn, A., N. Zaller, S. Dickman, C. Trimbur, A. Nijhawan, and J. D. Rich. 2009. Methadone and buprenorphine prescribing and referral practices in U.S. prison systems: Results from a nationwide survey. *Drug and Alcohol Dependence* 105(1–2):83–88.

Olsen, Y., and J. M. Sharfstein. 2014. Confronting the stigma of opioid use disorder—and its treatment. *JAMA* 311(14):1393–1394.

ONDCP (Office of National Drug Control Policy). 2017. *Changing the language of addiction*. https://www.whitehouse.gov/sites/whitehouse.gov/files/images/Memo%20-%20Changing%20Federal%20Terminology%20Regrading%20Substance%20Use%20and%20Substance%20Use%20Disorders.pdf (accessed February 12, 2019).

Patterson Silver Wolf, D. A. 2015. Factors influencing the implementation of a brief alcohol screening and educational intervention in social settings not specializing in addiction services. *Social Work in Health Care* 54(4):345–364.

Patterson Silver Wolf, D. A., C. van den Berk-Clark, S.-L. Williams, and C. N. Dulmus. 2017. Are therapists likely to use a new empirically supported treatment if required? *Journal of Social Work* 18(6):666–678.

Pincus, H. A., S. H. Scholle, B. Spaeth-Rublee, K. A. Hepner, and J. Brown. 2016. Quality measures for mental health and substance use: Gaps, opportunities, and challenges. *Health Affairs* 35:1000–1008.

Quest, T. L., J. O. Merrill, J. Roll, A. J. Saxon, and R. A. Rosenblatt. 2012. Buprenorphine therapy for opioid addiction in rural Washington: The experience of the early adopters. *Journal on Opioid Management* 8(1):29–38.

Rich, J. D., A. E. Boutwell, D. C. Shield, R. G. Key, M. McKenzie, J. G. Clarke, and P. D. Friedmann. 2005. Attitudes and practices regarding the use of methadone in U.S. state and federal prisons. *Journal of Urban Health* 82(3):411–419.

Rosen, D. L., D. M. Dumont, A. M. Cislo, B. W. Brockmann, A. Traver, and J. D. Rich. 2014. Medicaid policies and practices in U.S. state prison systems. *American Journal of Public Health* 104(3):418–420.

Rosenblatt, R. A., C. H. Andrilla, M. Catlin, and E. H. Larson. 2015. Geographic and specialty distribution of us physicians trained to treat opioid use disorder. *Annals of Family Medicine* 13(1):23–26.

Saloner, B., J. Levin, H. Chang, C. Jones, and G. Alexander. 2018. Changes in buprenorphine-naloxone and opioid pain reliever prescriptions after the Affordable Care Act Medicaid expansion. *JAMA Network Open* 1(4):e181588.

Samet, J. H., M. Botticelli, and M. Bharel. 2018. Methadone in primary care—One small step for Congress, one giant leap for addiction treatment. *New England Journal of Medicine* 379(1):7–8.

SAMHSA (Substance Abuse and Mental Health Services Administration). 2016. *Behavioral health spending and use accounts 1986–2014*. Rockville, MD: Substance Abuse and Mental Health Services Administration. https://store.samhsa.gov/system/files/sma16-4975.pdf (accessed February 12, 2019).

SAMHSA. 2018. *42 CFR part 2 confidentiality of substance use disorder patient records*. Rockville, MD: Substance Abuse and Mental Health Services Administration. https://www.samhsa.gov/health-information-technology/laws-regulations-guidelines (accessed Februrary 22, 2019).

Schwartz, R. P., D. A. Highfield, J. H. Jaffe, J. V. Brady, C. B. Butler, C. O. Rouse, J. M. Callaman, K. E. O'Grady, and R. J. Battjes. 2006. A randomized controlled trial of interim methadone maintenance. *Archives of General Psychiatry* 63(1):102–109.

Schwartz, R. P., S. M. Kelly, K. E. O'Grady, D. Gandhi, and J. H. Jaffe. 2012. Randomized trial of standard methadone treatment compared to initiating methadone without counseling: 12-month findings. *Addiction* 107(5):943–952.

Semple, S. J., I. Grant, and T. L. Patterson. 2005. Utilization of drug treatment programs by methamphetamine users: The role of social stigma. *American Journal of Addiction* 14(4):367–380.

Sharp, A., A. Jones, J. Sherwood, O. Kutsa, B. Honermann, and G. Millett. 2018. Impact of Medicaid expansion on access to opioid analgesic medications and medication-assisted treatment. *American Journal of Public Health* 108(5):642–648.

Singer, M., and J. B. Page. 2014. *The social value of drug addicts: Uses of the useless*. Walnut Creek, CA: Left Coast Press, Inc.

Somers, S. A., E. Nicolella, A. Hamblin, S. M. McMahon, C. Heiss, and B. W. Brockmann. 2014. Medicaid expansion: Considerations for states regarding newly eligible jail-involved individuals. *Health Affairs (Millwood)* 33(3):455–461.

Somers, B. D., C. E. Fry, R. J. Blendon, A. M. Epstein. 2018. New approaches in medicaid: Work requirements, health davings sccounts, snd health vare sccess. *Health Affairs (Millwood)* 37(7):1099–1108.

Stringer, K. L., and E. H. Baker. 2018. Stigma as a barrier to substance abuse treatment among those with unmet need: An analysis of parenthood and marital status. *Journal of Family Issues* 39(1):3–27.

Stuart, E. A., C. L. Barry, J. M. Donohue, S. F. Greenfield, K. Duckworth, Z. Song, R. Mechanic, E. M. Kouri, C. Ebnesajjad, M. E. Chernew, and H. A. Huskamp. 2017. Effects of accountable care and payment reform on substance use disorder treatment: Evidence from the initial 3 years of the alternative quality contract. *Addiction* 112:124–133.

Thomas, C. P., S. Reif, S. Haq, S. S. Wallack, A. Hoyt, and G. A. Ritter. 2008. Use of buprenorphine for addiction treatment: Perspectives of addiction specialists and general psychiatrists. *Psychiatric Services* 59(8):909–916.

Thomas, C. P., D. W. Garnick, C. M. Horgan, F. McCorry, A. Gmyrek, M. Chalk, D. Gastfriend, S. G. Rinaldo, J. Albright, V. A. Capoccia, A. Harris, H. Harwood, P. Greenberg, T. L. Mark, H. Un, M. T. Oros, M. Stringer, and J. Thatcher. 2011. Advancing performance measures for use of medications in substance abuse treatment. *Journal of Substance Abuse Treatment* 40:35–43.

van Boekel, L. C., E. P. M. Brouwers, J. van Weeghel, and H. F. L. Garretsen. 2013. Stigma among health professionals towards patients with substance use disorders and its consequences for healthcare delivery: Systematic review. *Drug and Alcohol Dependence* 131:23–35.

Volkow, N. D., T. R. Frieden, P. S. Hyde, and S. S. Cha. 2014. Medication-assisted therapies—Tackling the opioid-overdose epidemic. *New England Journal of Medicine* 370(22):2063–2066.

Wakeman, S. E. 2017. Medications for addiction treatment: Changing language to improve care. *Journal of Addiction Medicine* 11:1–2.

Wakeman, S. E., and M. L. Barnett. 2018. Primary care and the opioid-overdose crisis—Buprenorphine myths and realities. *New England Journal of Medicine* 379(1):1–4.

Wang, P. S., P. Berglund, M. Olfson, H. A. Pincus, K. B. Wells, and R. C. Kessler. 2005. Failure and delay in initial treatment contact after first onset of mental disorders in the national comorbidity survey replication. *Archives of General Psychiatry* 62(6):603–613.

Wen, H., J. R. Cummings, J. M. Hockenberry, L. M. Gaydos, and B. G. Druss. 2013. State parity laws and access to treatment for substance use disorder in the United States: Implications for federal parity legislation. *JAMA Psychiatry* 70(12):1355–1362.

Wen, H., J. M. Hockenberry, T. F. Borders, and B. G. Druss. 2017. Impact of Medicaid expansion on Medicaid-covered utilization of buprenorphine for opioid use disorder treatment. *Medical Care* 55(4):336–341.

Wittman, F. D., D. L. Polcin, and D. Sheridan. 2017. The architecture of recovery: Two kinds of housing assistance for chronic homeless persons with substance use disorders. *Drugs and Alcohol Today* 17(3):157–167.

Woo, J., A. Bhalerao, M. Bawor, M. Bhatt, B. Dennis, N. Mouravska, L. Zielinski, and Z. Samaan. 2017. "Don't judge a book by its cover": A qualitative study of methadone patients' experiences of stigma. *Substance Abuse: Research and Treatment* 11:PMC5398333.

Yancovitz, S. R., D. C. Des Jarlais, N. P. Peyser, E. Drew, P. Friedmann, H. L. Trigg, and J. W. Robinson. 1991. A randomized trial of an interim methadone maintenance clinic. *American Journal of Public Health* 81(9):1185–1191.

Zur, J., and J. Tolbert. 2018. *The opioid epidemic and Medicaid's role in facilitating access to treatment*. Kaiser Family Foundation. April 11. https://www.kff.org/medicaid/issue-brief/the-opioid-epidemic-and-medicaids-role-in-facilitating-access-to-treatment (accessed February 21, 2019).

Appendix A

Study Approach and Methods

In response to a request by the National Institute on Drug Abuse and the Substance Abuse and Mental Health Services Administration, the National Academies of Sciences, Engineering, and Medicine's Committee on Medication-Assisted Treatment for Opioid Use Disorder was charged with reviewing and evaluating the evidence base on medication-assisted treatment (MAT) for opioid use disorder (OUD), including the range of parameters for effective delivery of MAT, challenges with implementation and uptake, and additional research needs. The committee's final report will inform patients, providers, policy makers, and the public on the state of the evidence and knowledge gaps regarding treatment for OUD.

COMMITTEE EXPERTISE

The National Academies convened a 14-member ad hoc committee of experts in the fields of neurobiology, pharmacology, addiction medicine, psychology, social work, nursing, health policy, and epidemiology to respond to the charge by drawing on their experience and knowledge in the treatment of OUD. The committee also included individuals with lived experience, one as a patient and one as a family member of a person with OUD.

MEETINGS AND INFORMATION-GATHERING ACTIVITIES

The committee deliberated from October 2018 to January 2019, during the course of which it held two in-person meetings in October and

December. The October meeting included portions open to the public. The agenda of the open session appears in Appendix B. The committee meeting in December 2018 was held in closed session. The committee also communicated as needed via email and video conference.

To inform its deliberations the committee gathered information through a variety of mechanisms: (1) one 1.5-day workshop with open public sessions; (2) one open public comment session during its October meeting; (3) literature reviews of the medical, scientific, and policy issues; (4) solicitation and consideration of written statements from stakeholders and members of the public through the committee's Current Projects System website and by coordinated e-mail outreach; and (5) personal communication among committee members and staff and individuals who have been directly involved in or have special knowledge of the issues under consideration. Comments submitted to the committee can be found in the Public Access File.

LITERATURE AND PRESS REVIEW

The committee and staff conducted a series of literature searches that concentrated on journals found in the following databases: Embase, Medline, Cochrane Database of Systematic Reviews, PubMed, Scopus, and Web of Science. The articles obtained by use of the search terms were reviewed for their relevance to the committee's charge. Search terms for the committee's literature searches are detailed below. This does not represent an exhaustive list of the research conducted. Other targeted literature reviews were conducted throughout the committee's deliberations as novel issues arose and research gaps were identified.

Search Parameter

- Date parameters: 1940–current
- Include international citations—foreign languages

Publication Types

Case studies, clinical trials, cohort studies, grey literature, peer-reviewed literature, randomized clinical trials, randomized controlled trials, systematic reviews.

Agency Reviews

Academy of Managed Care Pharmacy, Addiction Medicine Foundation, Agency for Healthcare Research and Quality, American Psychological

Association, American Society of Addiction Medicine, Centers for Medicare & Medicaid Services, Drug Enforcement Administration, National Council of State Legislatures, National Institutes of Health, Substance Abuse and Mental Health Services Administration, U.S. Centers for Disease Control and Prevention, U.S. Department of Justice, U.S. Food and Drug Administration.

Opioid Use Disorder Related Terms

Opioid addiction, opioid-related disorder (MeSH), opioid use disorder, analgesics, opioid (MeSH), opiate, butorphanol, codeine, fentanyl, hydrocodone, levorphanol, meperidine, methodone, morphine, oxycodone, oxymorphone, tapentadol, heroin, fentayl-laced heroin, medication-assisted treatment, opioid substitution treatment, buprenorphinne, methadone, naltrexone, anti-drug vaccines, anti-opioid vaccination, cannabinoids, marijuana, diacetylmorphine, extended-release morphine, hydromorphone, injectable opioid agonist therapy, levo-alpha acetyl, supervised injectable heroin, sustained-release morphine, discontinuation, duration of treatment, medication adherence (MeSH), medication compliance (MeSH), medication counseling, medication non-adherence, medication non-compliance (MeSH), pharmaceutical therapy, tapering, cost effectiveness (MeSH), demographic effectiveness (MeSH), effectiveness treatment (MeSH), medically assisted, medically observed, out-patient treatment, out-patients, program effectiveness (MeSH), treatment effectiveness (MeSH), addiction, behavior, addiction (MeSH), communicable diseases (MeSH), comorbidities, depression, hepatitis (MeSH), infectious diseases, substance abuse, substance-related disorders (MeSH), acceptance and commitment therapy (MeSH), cognitive therapy (MeSH), counseling (MeSH), directive counseling (MeSH), marijuana treatment, addiction centers, delivery of health care (MeSH), drug treatment centers (MeSH), duration of treatment, emergency room, health care delivery (MeSH), health services accessibility, interventions, primary health care (MeSH), adolescent, continental population groups (MeSH), minority health, pregnant women, prisoners/incarcerated, rural populations, urban populations, vulnerable populations (MeSH), health disparities, health care disparities, medically underserved, medically underserved area (MeSH), social determinants of health, socioeconomic factors, crisis intervention, early intervention, infrastructure, physician shortage, regulations, addiction medicine training, clinician training (physician, nurse, physician assistant), education (MeSH), medical school curriculum training and materials, opioid-related education, physician training, social workers, medication availability, medical supply shortage, physician shortage area (MeSH), stigma, social stigma (MeSH), health insurance, insurance, reimbursement, reimbursement mechanisms (MeSH), drug crime

policy, federal/state funding, law enforcement, regulations, sentencing and corrections legislation, treatment courts, clinical trials—links to clinical trials, future opiate substitution treatment.

Appendix B

Public Workshop Agenda

Keck Center
E Street Conference Room
500 Fifth Street, NW, Washington, DC 20001

DAY 1: OCTOBER 29, 2018
OPEN SESSION

1:00pm **Opening Remarks to Public Audience**

- **Alan I. Leshner, Ph.D.,** Committee Chair
  Chief Executive Officer Emeritus
  American Association for the Advancement of Science

1:10pm **Presentation by Sponsoring Agencies**

- **Jack B. Stein, M.S.W., Ph.D.**
  Director, Office of Science Policy and Communications
  National Institute on Drug Abuse

- **Deepa Avula, M.P.H.**
  Director, Office of Financial Resources
  Substance Abuse and Mental Health Services Administration

- **Rebecca Baker, Ph.D.**
  Special Assistant to the Director
  National Institutes of Health

1:30pm **Sponsor Q&A with Committee**

- **Alan I. Leshner,** Committee Chair

Time to ask clarifying questions to understand scope and charge of the Statement of Task

2:30pm **Adjourn Open Session**

DAY 2: OCTOBER 30, 2018
OPEN SESSION

8:30am **Welcome and Opening Remarks**

- **Alan I. Leshner,** Committee Chair
  Chief Executive Officer Emeritus
  American Association for the Advancement of Science

- **Victor J. Dzau,** National Academy of Medicine (via video)

SESSION 1: FEDERAL INITIATIVES

105-minute session (brief 5- to 7-minute panelist presentations followed by moderated discussion and Q&A)

8:45am Objectives:

- Discuss current federal efforts to improve treatment for opioid use disorder (OUD) and access to medication-assisted treatment and hear perspectives from the study sponsors, National Institute on Drug Abuse and Substance Abuse and Mental Health Services Administration.

Moderator:

- **Alan I. Leshner,** Committee Chair
  Chief Executive Officer Emeritus
  American Association for the Advancement of Science

Panelists:

- **Nora Volkow,** National Institute on Drug Abuse
- **Deepa Avula,** Substance Abuse and Mental Health Services Administration
- **Molly Evans,** U.S. Centers for Disease Control and Prevention
- **Judith Steinberg,** Health Resources and Services Administration
- **Rigo Roca,** U.S. Food and Drug Administration

10:30am BREAK

SESSION 2: CURRENT EVIDENCE AND PRACTICE ON MEDICATION FOR TREATING OPIOID USE DISORDER

120 minutes (25-minute opening presentation followed by moderated panel discussion)

10:45am Objectives:

- Discuss current evidence on the effectiveness of specific medications used to treat OUD.
- Identify evidence gaps that might contribute to limited effectiveness of specific medications or limit the use of medications in treating OUD, i.e., dosing ranges, optimal duration of treatments, discontinuation, optimal duration of tapering medication, and real-world evidence on patient experiences and preferences.
- For each medication, examine the regulations, infrastructure, and care settings required for delivery of specific medications for OUD, and explore how this influences patient and provider preference when selecting treatment.
- Discuss the evidence for behavioral counseling as a component of treatment for OUD. Are the current requirements for counseling evidence-based?
- Identify barriers to the use of specific medications, including any long-term side effects of medications for treating OUD and the perception and stigma of treatment options by patients, providers, the general public, and law enforcement.

Moderator:

- **Kathleen Carroll,** Yale School of Medicine

Opening Presentation:

- **Charles O'Brien,** University of Pennsylvania

Panelists:

- **Gavin Bart,** University of Minnesota
- **Michelle Lofwall,** University of Kentucky
- **Adam Bisaga,** Columbia University Medical Center
- **John Brooklyn,** University of Vermont
- **Maia Szalavitz,** American reporter and author

12:45pm LUNCH

SESSION 3: IMPLEMENTATION AND UPTAKE: OPPORTUNITIES AND BARRIERS

1:45pm **Panel 3a: Opportunities and Barriers—Education and Training to Expand Treatment**

(Brief 5- to 7-minute panelist presentations followed by moderated discussion and Q&A)

Objectives:

- Examine the currently required education and training for providers treating OUD, and identify best practices and hurdles to achieving the required workforce to treat OUD.
- Explore the makeup of an ideal OUD treatment workforce, and discuss how this workforce may change based on care settings, populations, regions, and availability of medication for the treatment of OUD.
- Consider educational requirements for clinicians (surgical services, primary care, emergency departments, pharmacists), counselors, social workers, and others.
- Discuss what patient and family education or resources should be provided.
- Identify best practices and education for policy makers, law enforcement, the public, and other stakeholders.

Moderator:
Chinazo Cunningham, Albert Einstein College of Medicine

Panelists:

- **Jeanette Tetrault,** Yale University
- **Stephen Patrick,** Vanderbilt University
- **Eugenia Oviedo-Joekes,** University of British Columbia
- **Jules Netherland,** Drug Policy Alliance
- **Kathleen Johnson,** Advocates for Opioid Recovery

3:15pm BREAK

3:30pm **Panel 3b: Opportunities and Barriers—Health Care Delivery, Payment Approaches, and Economics Measures to Improve Treatment of OUD**

90 minutes (15-minute opening presentation followed by moderated panel discussion)

Objectives:

- Discuss how health care access and delivery affect patient access to medications to treat OUD; consider regulations around hospital capacity, administrative burdens, and the tight regulation of medical products.
- Explore the cost, reimbursement, and coverage of medications to treat OUD, and discuss measures to help facilitate quality improvement and access.
- Examine regulatory differences of for-profit versus nonprofit treatment providers.

Moderator:

- **Colleen Barry,** Johns Hopkins Bloomberg School of Public Health

Opening Presentation:

- **Richard Frank,** Harvard University

Panelists:

- **Allan Coukell,** Pew Charitable Trust
- **Katrina King,** George Mason University
- **Yngvild Olson,** Medical Director, Institutes for Behavior Resources, Inc.

5:00pm **Day 1 Recap and Closing Remarks**

- **Alan I. Leshner,** Committee Chair, Chief Executive Officer Emeritus, American Association for the Advancement of Science

5:15pm **Adjourn**

DAY 3: OCTOBER 31, 2018
OPEN SESSION

8:30am **Welcome and Opening Remarks**

- **Alan I. Leshner,** Committee Chair
  Chief Executive Officer Emeritus
  American Association for the Advancement of Science

8:45am **Panel 3c: Opportunities and Barriers—Social Determinants of Health and Treatment for OUD**

(Brief 5- to 7-minute panelist presentations followed by moderated discussion and Q&A)

Objectives:

- Explore the impact of comorbidities on treatment and how this may affect the uptake and overall effectiveness of medications to treat OUD.
- Consider how pregnancy, age, race, gender, genetic variables, mental health, chronic pain, and other factors may influence treatment.
- Identify further evidence needed to better deliver culturally appropriate care and serve diverse populations.

Moderator:

- **David Patterson Silver Wolf,** Washington University

Panelists:

- **Helena B. Hansen,** New York University
- **Josiah Rich,** Brown University
- **Anand Kumar,** University of Illinois at Chicago
- **Mishka Terplan,** Virginia Commonwealth University

10:15am BREAK

SESSION 4: KNOWLEDGE GAPS—FUTURE RESEARCH AND NEXT STEPS

90 minute session (brief 5- to 7-minute panelist presentations followed by moderated discussion and Q&A)

10:30am Objectives:

- Discuss required research on U.S. Food and Drug Administration (FDA)-approved and non-FDA-approved medications for the treatment of OUD; consider patient preferences, delivery mechanisms, patient population (e.g., demographics or severity of OUD), and how different treatment settings may affect the research required.
- Identify patient outcome measures and process measures to facilitate the development of best practices for treating OUD.
- Identify research needs and policy changes to advance treatment and recovery.

Moderator:

- **Yasmin Hurd,** Icahn School of Medicine at Mount Sinai

Panelists:

- **Sharon Walsh,** University of Kentucky
- **Gail D'Onofrio,** Yale University
- **Jonathan H. Watanabe,** University of California, San Diego
- **Jessica Hulsey Nickel,** Addiction Policy Forum

SESSION 5: PUBLIC COMMENT

30-minute session

12:00pm Objective:

- Members of the public are invited to sign up to provide comments on the workshop topic (3 minutes each)

Moderator:

- **Alan I. Leshner,** Committee Chair
  Chief Executive Officer Emeritus
  American Association for the Advancement of Science

12:30pm **Meeting Recap and Closing Remarks**

- **Alan I. Leshner,** Committee Chair
  Chief Executive Officer Emeritus
  American Association for the Advancement of Science

12:45pm **Adjourn**

Appendix C

Biographical Sketches of Committee Members

Alan I. Leshner, Ph.D. (NAM) (*Chair*), is the chief executive officer, emeritus, of the American Association for the Advancement of Science (AAAS) and the former executive publisher of the *Science* family of journals. Before joining AAAS, Dr. Leshner was the director of the National Institute on Drug Abuse at the National Institutes of Health. He also served as the deputy director and acting director of the National Institute of Mental Health and in several roles at the National Science Foundation. Before joining the government, Dr. Leshner was a professor of psychology at Bucknell University. Dr. Leshner is an elected fellow of AAAS, the American Academy of Arts and Sciences, the National Academy of Public Administration, and many other professional organizations. He is a member of and served on the governing council of the National Academy of Medicine. He served two terms on the National Science Board, appointed first by President Bush and then reappointed by President Obama. Dr. Leshner received Ph.D. and M.S. degrees in physiological psychology from Rutgers University and an A.B. in psychology from Franklin & Marshall College. Dr. Leshner has received many honors and awards, including the Walsh McDermott Medal from the National Academy of Medicine and seven honorary doctor of science degrees.

Huda Akil, Ph.D. (NAS/NAM), is the Gardner Quarton Distinguished University Professor of Neuroscience and Psychiatry and the co-director of the Molecular and Behavioral Neuroscience Institute at the University of Michigan. Research in the Akil laboratory is focused on understanding the brain biology of emotions, including pain, anxiety, depression, and substance

abuse. Her early work provided the first physiological evidence for a role of endogenous opioids in the brain and demonstrated that endorphins are activated by stress to block pain, a phenomenon termed stress-induced analgesia. She and her colleagues demonstrated that genes that encode the natural opioids produce multiple products in the brain and that these products act in a coordinated manner to modify a wide range of behaviors, including the control of feeding and the response to stress, pain, and drugs of abuse.

Dr. Akil collaborated with Stanley J. Watson in a series of studies, including the cloning of two types of opioid receptors and the extensive characterization of the brain anatomy of the opioid peptides and receptors. Her group conducted extensive structure–function analyses defining the molecular basis of selectivity and high-affinity binding of endorphins and opioid drugs at the different subtypes of opioid receptors.

A major focus of her current research program is on establishing animal models to uncover the genetic and developmental bases of temperament, and the implications of these inborn differences for vulnerability to clinical depression and to substance abuse disorders.

Colleen Barry, Ph.D., is the Fred and Julie Soper Professor and the chair of the Department of Health Policy and Management at the Johns Hopkins Bloomberg School of Public Health. She has a joint appointment in the Department of Mental Health. Dr. Barry's research focuses on how health and social policies can affect a range of outcomes for individuals with mental illness and substance use disorders (SUDs), including access to medical care and social services, care quality, health care spending, financial protection, and mortality. She is involved in numerous research studies examining the implications of health insurance expansions and health care delivery system reform efforts on the treatment of mental illness and SUDs. She also conducts empirical research to understand how communication strategies influence public attitudes about opioid addiction, mental illness, gun policy, and obesity and food policy. One focus of this work is to identify evidence-based approaches to reducing stigma. She has authored more than 150 peer-reviewed articles on these topics. Dr. Barry is founding co-director (with Elizabeth Stuart) of the Johns Hopkins Center for Mental Health and Addiction Policy Research and is a core faculty member in the Johns Hopkins Center for Gun Policy and Research. Dr. Barry received her Ph.D. in health policy from Harvard University and her master's degree in public policy from the John F. Kennedy School of Government at Harvard University.

Kathleen Carroll, Ph.D., is the Albert E. Kent Professor of Psychiatry at the Yale School of Medicine. She graduated summa cum laude from Duke University, received her Ph.D. in clinical psychology in 1988 from the

University of Minnesota, and completed her pre-doctoral training at the Yale School of Medicine's Division of Addictions, where she was promoted to professor in 2002. She is the principal investigator of the Center for Psychotherapy Development at Yale, the National Institute on Drug Abuse's (NIDA's) only center devoted to behavioral therapies research, and since 1999 she has been the principal investigator of the New England Consortium Node of NIDA's Clinical Trials Network (merging with Dr. Roger Weiss's northern New England node in 2008). Dr. Carroll is the author of more than 300 peer-reviewed publications as well as numerous chapters and books. Her research has focused on the development and evaluation of behavioral treatments and combinations of behavioral therapies and pharmacotherapies, with an emphasis on improving the quality and rigor of clinical efficacy research in the addictions. Dr. Carroll received a National Institutes of Health Method to Extend Research in Time award in 2003 for her work on developing Web-based cognitive–behavioral therapy.

Chinazo Cunningham, M.D., is a professor at the Albert Einstein College of Medicine. Since 1998, Dr. Cunningham has been providing care, developing programs, and conducting research focused on people who use drugs. She has collaborated with community-based organizations to develop unique and innovative programs. Parallel with program development, her research has focused on improving access to care, the use of health care services, and health outcomes. Dr. Cunningham has published more than 100 articles and has been the principal investigator on numerous grants funded by the National Institutes of Health (NIH), the U.S. Centers for Disease Control and Prevention (CDC), the Health Resources and Services Administration, foundations, and local and state departments of health. Dr. Cunningham has served on numerous national advisory committees, including serving as the chair of New York State Department of Health's Substance Use Guidelines Committee; a member and chair of NIH's Behavioral and Social Consequences of HIV/AIDS Study Section; and a member of CDC's board of scientific counselors of the National Center for Injury Prevention and Control. Dr. Cunningham's husband is employed by and owns stock in Quest Diagnostics.

Walter Ginter is the project director of the Medication Assisted Recovery Support (M.A.R.S.) Project. The M.A.R.S. Project is funded by the Substance Abuse and Mental Health Services Administration's Center for Substance Abuse Treatment. It is the only federal project designed to provide peer recovery support to persons whose recovery from opiate addiction is assisted by medication. It is in collaboration with the Division of Substance Abuse at the Albert Einstein College of Medicine, Yeshiva University, and the National Alliance for Medication Assisted (NAMA)

Recovery. He was formerly on the board of directors of Faces and Voices of Recovery. Mr. Ginter is the director of training and certification at NAMA Recovery. He is a planning partner for National Recovery Month and a member of the Methadone Treatment Advisory Group of the New York State Office of Alcoholism and Substance Abuse Services (OASAS) and the New York State OASAS Recovery Implementation Team.

Traci Green, Ph.D., M.Sc., is an associate professor of emergency medicine and community health sciences at the Boston University Schools of Medicine and Public Health, the deputy director of the Boston Medical Center Injury Prevention Center, and an adjunct associate professor of emergency medicine at the Warren Alpert Medical School of Brown University. Dr. Green is an epidemiologist whose research focuses on drug use, opioid addiction, and drug-related injury. Specifically, the areas in which she is most interested and to which she has contributed include the intersecting worlds of HIV infection and drug use, the non-medical use of prescription drugs, corrections health, drug policy, and opioid overdose prevention and intervention. She earned a master of science in epidemiology and biostatistics from McGill University and a Ph.D. in epidemiology from Yale University where she was both a Center for Interdisciplinary Research on AIDS pre-doctoral fellow and an individual Kirschstein–National Research Services Award pre-doctoral fellow. She helped design the ASI-MV®, a real-time illicit and prescription misuse surveillance system developed by Inflexxion, Inc. Dr. Green helped co-found www.prescribetoprevent.org for prescribers and pharmacists and its companion site, www.prevent-protect.org, for families, patients, and community organizations. She serves as an advisor to the Rhode Island governor on addiction and overdose, and consults for the U.S. Centers for Disease Control and Prevention (CDC) and the High Intensity Drug Trafficking Areas on public health and public safety opportunities. She served on the board of scientific counselors for CDC's National Center for Injury Prevention and Control and on the National Academies of Sciences, Engineering, and Medicine's Committee on Pain Management and Regulatory Strategies to Address Prescription Opioid Abuse. Her research is supported by CDC, the National Institute on Drug Abuse, the Agency for Healthcare Research and Quality, the Patient-Centered Outcomes Research Institute, the Bloomberg American Health Initiative, and the U.S. Department of Justice.

Yasmin Hurd, Ph.D. (NAM), is the Ward-Coleman Chair of Translational Neuroscience and the director of the Addiction Institute at Mount Sinai. Dr. Hurd's multidisciplinary research investigates the neurobiology underlying addiction disorders and related psychiatric illnesses. A translational

approach is used to examine molecular and neurochemical events in the human brain and comparable animal models in order to ascertain neurobiological correlates of behavior. Her basic science studies are complemented by human clinical laboratory investigations in patients with substance use disorders focused on the development of new treatment interventions.

Alan Jette, PT, Ph.D., M.P.H., FAPTA (NAM), is a professor of rehabilitation science in the Ph.D. in Rehabilitation Sciences program and in the Department of Physical Therapy at the MGH Institute of Health Professions. Dr. Jette is also a professor and dean emeritus at Boston University. Dr. Jette is a physical therapist and an internationally recognized expert in the measurement of function and disability. He has developed numerous instruments that assess function and disability and has published numerous articles on these topics in the rehabilitation, geriatrics, and public health literature.

Over the past 30 years, Dr. Jette has received a total of 54 grants and fellowships from such agencies as the National Institutes of Health (multiple divisions), Robert Wood Johnson Foundation, and the National Arthritis Foundation. His current research interests include the measurement, epidemiology, and prevention of disability and the development and dissemination of contemporary outcome measurement instruments to evaluate the quality of health care. He also has applied his research to randomized clinical trials to reduce disability in older adults using cognitive–behavioral strategies, exercise training, and programs to reduce fear of falling. He furthermore developed and tested innovative strategies to disseminate these programs to the wider community.

From 2005 to 2007 Dr. Jette chaired the Institute of Medicine (IOM) project The Future of Disability in America. Building on the 1991 landmark IOM report *Disability in America*, the IOM panel presented updated developments since that report's publication and highlighted future priorities for the nation. The panel's report was released in 2007. In 2013, Dr. Jette was elected to the National Academy of Medicine. He currently serves as editor-in-chief of the journal *Physical Therapy*.

Laura R. Lander, M.S.W., is an associate professor, social work section chief, and addiction therapist in the Department of Behavioral Medicine and Psychiatry and the Department of Neuroscience at West Virginia University's School of Medicine. She graduated with a master's in social work from Columbia University and currently holds licensure as an independent clinical social worker under the West Virginia Board of Social Work Licensure. She previously served as the clinical coordinator of the Child Outpatient Clinic at McLean Hospital in Belmont, Massachusetts, and was the director of adult mental health services at the Pederson Krag Center

in Smithtown, New York. She is a member of the National Association of Social Workers and the National Association for Addiction Professionals.

David Patterson Silver Wolf, Ph.D., is an associate professor at Washington University in St. Louis' Brown School of Social Work. Dr. Patterson Silver Wolf is a faculty scholar in the Washington University Institute for Public Health; co-director of the Collaboration on Race, Inequality, and Social Mobility in America; and the research director in the Buder Center, and he serves as training faculty for two National Institutes of Health–funded (T32) training programs at the Brown School, including the Transdisciplinary Training in Addictions Research program of the National Institute on Drug Abuse.

Before entering academics, he spent more than 15 years providing clinical services in the substance use disorder treatment field and is a person who has sustained a life in recovery since 1989. Dr. Patterson Silver Wolf investigates how to best implement evidence-based interventions and technologies into community-based services. He is leading a new technology start-up, Takoda (https://www.takoda.io), that develops tech tools to measure and monitor treatment performance. He is the director of the Community Academic Partnership on Addiction (CAPA) and is the chief research officer at the new CAPA Clinic, a St. Louis City addiction outpatient treatment program. The CAPA Clinic is incorporating and testing various performance-based practice technology tools to respond to the opioid epidemic and to improve addiction treatment outcomes.

Dr. Patterson Silver Wolf also studies factors that improve underrepresented minority college students' academic success and has developed a brief intervention that significantly increases college retention and grade point average.

Seun Ross, D.N.P., M.S.N., CRNP-F, NP-C, NEA-BC, is the director of nursing practice and work environment at the American Nurses Association. Dr. Ross is a published author and a lecturer on many topics within her research interests, which include evidence-based practice, workforce management, registered nurse (RN) work environment, competency, and developing and mentoring the novice RN. In her clinical experience as a hospital administrator and clinician, she worked with pregnant women where medication-assisted therapy was part of the treatment regimen. She is currently the president of IMBUE Foundation and the immediate past president of the Chi Zeta Chapter of Sigma Theta Tau Nursing Honor Society and a member of the Academy of Healthcare Executives, and she holds certifications as a family nurse practitioner and nurse executive–advanced.

Scott Steiger, M.D., is an associate clinical professor of medicine and psychiatry at the University of California, San Francisco, and is board certified in both internal medicine and addiction medicine. Currently serving as the deputy medical director of the Opiate Treatment Outpatient Program at San Francisco General, he helps direct the "medication-assisted" treatment of approximately 600 patients with opioid use disorder, more than half of whom are experiencing homelessness. He has extensive clinical and teaching experience in the treatment of opiate use disorder with all U.S. Food and Drug Administration–approved medications in the safety net primary care, acute care hospital, and specialty licensed opiate treatment program settings.

David Vlahov, Ph.D., RN FAAN (NAM), is the associate dean for research and a professor of nursing at the Yale School of Nursing with a secondary appointment as a professor of epidemiology at the Yale School of Public Health. He served as the principal investigator of the AIDS Link to Intravenous Experiences (ALIVE) study for its first 15 years; the study recruited 2,921 injection drug users outside of treatment settings in 1988–1989 and followed them semiannually. The study has continued and recently completed its 30th year of follow-up. This study was originally designed to address the epidemiology and natural history of HIV infection among drug users, but it expanded to include detailed investigations of many other medical consequences of drug use through clinical endpoints and mortality. The study provided data on the natural history of drug use that shape patterns of drug use, including medically assisted therapies. ALIVE has been more than simply a natural history study, and its data have been used to evaluate programs and policies that affect population health. For this study, Dr. Vlahov received a National Institutes of Health Method to Extend Research in Time award. Dr. Vlahov has been the principal investigator of several other longitudinal studies of drug users, including the U.S. Centers for Disease Control and Prevention's HIV Epidemiology Research study of HIV infection in women, with half reporting substance use, and the REACH longitudinal study of HIV in adolescents and young adult drug users. In addition, Dr. Vlahov has completed studies of infectious disease prevalence and incidence in correctional settings as well as studies of reentry challenges. He served as the director of the Center for Urban Epidemiologic Studies at The New York Academy of Medicine, where he was the academic lead and principal investigator for the Harlem Community–Academic Partnership, which completed community-based participatory research to evaluate outreach programs for substance users. He served on the National Advisory Council on Drug Abuse and on the board of health for New York City. He is an expert more broadly in urban health, serving as editor of the *Journal of Urban Health* and founding president for the

International Society for Urban Health. He has edited 4 books and published more than 660 papers. He is a member of the National Academy of Medicine and the Johns Hopkins Society of Scholars and is a fellow of the American Academy of Nursing. He earned his undergraduate degrees at Earlham College and the University of Maryland and his doctoral degree at the Johns Hopkins Bloomberg School of Public Health.