TIP 63

MEDICATIONS FOR OPIOID USE DISORDER

Treatment Improvement Protocol 63

For Healthcare and Addiction Professionals, Policymakers, Patients, and Families

This TIP reviews three Food and Drug Administration-approved medications for opioid use disorder treatment—methadone, naltrexone, and buprenorphine—and the other strategies and services needed to support people in recovery.

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TIP 63

MEDICATIONS FOR OPIOID USE DISORDER

Executive Summary

For Healthcare and Addiction Professionals, Policymakers, Patients, and Families

The Executive Summary of this **Treatment Improvement Protocol** provides an overview on the use of the three Food and Drug Administration-approved medications used to treat opioid use disorder—methadone, naltrexone, and buprenorphine—and the other strategies and services needed to support recovery.

TIP Navigation

DEPARTMENT OF HEALTH & HUMAN SERVICES · USA

SAMHSA
Substance Abuse and Mental Health Services Administration

EXECUTIVE SUMMARY

Foreword

The Substance Abuse and Mental Health Services Administration (SAMHSA) is the U.S. Department of Health and Human Services agency that leads public health efforts to advance the behavioral health of the nation. SAMHSA's mission is to reduce the impact of substance abuse and mental illness on America's communities.

The Treatment Improvement Protocol (TIP) series fulfills SAMHSA's mission by providing science-based best-practice guidance to the behavioral health field. TIPs reflect careful consideration of all relevant clinical and health service research, demonstrated experience, and implementation requirements. Select nonfederal clinical researchers, service providers, program administrators, and patient advocates comprising each TIP's consensus panel discuss these factors, offering input on the TIP's specific topic in their areas of expertise to reach consensus on best practices. Field reviewers then assess draft content.

The talent, dedication, and hard work that TIP panelists and reviewers bring to this highly participatory process have helped bridge the gap between the promise of research and the needs of practicing clinicians and administrators to serve, in the most scientifically sound and effective ways, people in need of behavioral health services. We are grateful to all who have joined with us to contribute to advances in the behavioral health field.

Elinore F. McCance-Katz, M.D., Ph.D.
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Executive Summary

The goal of treatment for opioid addiction or opioid use disorder (OUD) is remission of the disorder leading to lasting recovery. Recovery is a process of change through which individuals improve their health and wellness, live self-directed lives, and strive to reach their full potential.[1] This Treatment Improvement Protocol (TIP) reviews the use of the three Food and Drug Administration (FDA)-approved medications used to treat OUD—methadone, naltrexone, and buprenorphine—and the other strategies and services needed to support recovery for people with OUD.

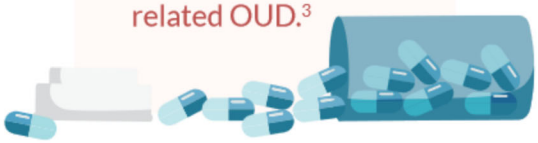
Introduction

Our nation faces a crisis of overdose deaths from opioids, including heroin, illicit fentanyl, and prescription opioids. These deaths represent a mere fraction of the total number of Americans harmed by opioid misuse and addiction. Many Americans now suffer daily from a chronic medical illness called "opioid addiction" or OUD (see the Glossary in Part 5 of this TIP for definitions). Healthcare professionals, treatment providers, and policymakers have a responsibility to expand access to evidence-based, effective care for people with OUD.

Estimated cost of the **OPIOID EPIDEMIC** was **$504 BILLION** in 2015.[2]

An expert panel developed the TIP's content based on a review of the literature and on their extensive experience in the field of addiction treatment. Other professionals also generously contributed their time and commitment to this project.

An estimated **1.8M AMERICANS** have OUD related to opioid painkillers; **626K** have heroin-related OUD.[3]



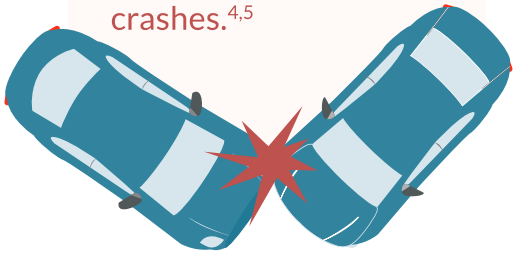
The TIP is divided into parts so that readers can easily find the material they need. Part 1 is a general introduction to providing medications for OUD and issues related to providing that treatment. Some readers may prefer to go directly to those parts most relevant to their areas of interest, but everyone is encouraged to read Part 1 to establish a shared understanding of key facts and issues covered in detail in this TIP.

Following is a summary of the TIP's overall main points and brief summaries of each of the five TIP parts.

Overall Key Messages

Addiction is a chronic, treatable illness. Opioid addiction, which generally corresponds with moderate to severe forms of OUD, often requires continuing care for effective treatment rather than an episodic, acute-care treatment approach.

Opioid overdose caused **42,249 DEATHS** nationwide in 2016—this exceeded the # caused by motor vehicle crashes.[4,5]



General principles of good care for chronic diseases can guide OUD treatment. Approaching OUD as a chronic illness can help providers deliver care that helps patients stabilize, achieve remission of symptoms, and establish and maintain recovery.

Patient-centered care empowers patients with information that helps them make better treatment decisions with the healthcare professionals involved in their care. Patients should receive information from their healthcare team that will help them understand OUD and the options for treating it, including treatment with FDA-approved medication.

Patients with OUD should have access to mental health services as needed, medical care, and addiction counseling, as well as recovery support services, to supplement treatment with medication.

The words you use to describe OUD and an individual with OUD are powerful. The TIP defines, uses, and encourages providers to adopt terminology that will not reinforce prejudice, negative attitudes, or discrimination.

There is no "one size fits all" approach to OUD treatment. Many people with OUD benefit from treatment with medication for varying lengths of time, including lifelong treatment. Ongoing outpatient medication treatment for OUD is linked to better retention and outcomes than treatment without medication. Even so, some people stop using opioids on their own; others recover through support groups or specialty treatment with or without medication.

The science demonstrating the effectiveness of medication for OUD is strong. For example, methadone, extended-release injectable naltrexone (XR-NTX), and buprenorphine were each found to be more effective in reducing illicit opioid use than no medication in randomized clinical trials, which are the gold standard for demonstrating efficacy in clinical medicine.[6,7,8,9,10] Methadone and buprenorphine treatment have also been associated with reduced risk of overdose death.[11,12,13,14,15]

This doesn't mean that remission and recovery occur only through medication. Some people achieve remission without OUD medication, just as some people can manage type 2 diabetes with exercise and diet alone. But just as it is inadvisable to deny people with diabetes the medication they need to help manage their illness, it is also not sound medical practice to deny people with OUD access to FDA-approved medications for their illness.

Medication for OUD should be successfully integrated with outpatient and residential treatment. Some patients may benefit from different levels of care at different points in their lives, such as outpatient counseling, intensive outpatient treatment, inpatient treatment, or long-term therapeutic communities. Patients treated in these settings should have access to OUD medications.

2.1 MILLION people in the U.S., ages 12 and older, had OUD involving **PRESCRIPTION OPIOIDS, HEROIN,** or both in 2016.[16]

Patients treated with medications for OUD can benefit from individualized psychosocial supports. These can be offered by patients' healthcare providers in the form of medication management and supportive counseling and/or by other providers offering adjunctive addiction counseling, recovery coaching, mental health services, and other services that may be needed by particular patients.

Expanding access to OUD medications is an important public health strategy.[17] The gap between the number of people needing opioid addiction treatment and the capacity to treat them with OUD medication is substantial. In 2012, the gap was estimated at nearly 1 million people, with about 80 percent of opioid treatment programs (OTPs) nationally operating at 80 percent capacity or greater.[18]

Improving access to treatment with OUD medications is crucial to closing the wide gap between treatment need and treatment availability, given the strong evidence of effectiveness for such treatments.[19]

Data indicate that medications for OUD are cost effective and cost beneficial.[20,21]

OPIOID-RELATED
EMERGENCY DEPARTMENT
visits nearly doubled from 2005–2014.[22]

Content Overview

The TIP is divided into parts to make the material more accessible according to the reader's interests.

Part 1: Introduction to Medications for Opioid Use Disorder Treatment

This part lays the groundwork for understanding treatment concepts discussed later in this TIP. The intended audience includes:

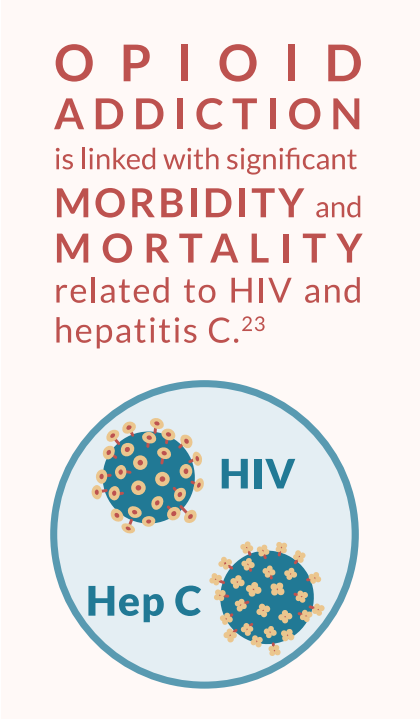
- Healthcare professionals (physicians, nurse practitioners, physician assistants, and nurses).
- Professionals who offer addiction counseling or mental health services.
- Peer support specialists.
- People needing treatment and their families.
- People in remission or recovery and their families.
- Hospital administrators.
- Policymakers.

In Part 1, readers will learn that:

- Increasing opioid overdose deaths, illicit opioid use, and prescription opioid misuse constitute a public health crisis.
- OUD medications reduce illicit opioid use, retain people in treatment, and reduce risk of opioid overdose death better than treatment with placebo or no medication.
- Only physicians, nurse practitioners, and physician assistants can prescribe buprenorphine for OUD. They must get a federal waiver to do so.
- Only federally certified, accredited OTPs can dispense methadone to treat OUD. OTPs can administer and dispense buprenorphine without a federal waiver.
- Any prescriber can offer naltrexone.
- OUD medication can be taken on a short- or long-term basis, including as part of medically supervised withdrawal and as maintenance treatment.
- Patients taking medication for OUD are considered to be in recovery.
- Several barriers contribute to the underuse of medication for OUD.

Part 2: Addressing Opioid Use Disorder in General Medical Settings

This part offers guidance on OUD screening, assessment, treatment, and referral. Part 2 is for healthcare professionals working in general medical settings with patients who have or are at risk for OUD.



In Part 2, readers will learn that:

- All healthcare practices should screen for alcohol, tobacco, and other substance misuse (including opioid misuse).
- Validated screening tools, symptom surveys, and other resources are readily available; this part lists many of them.
- When patients screen positive for risk of harm from substance use, practitioners should assess them using tools that determine whether substance use meets diagnostic criteria for a substance use disorder (SUD).
- Thorough assessment should address patients' medical, social, SUD, and family histories.
- Laboratory tests can inform treatment planning.
- Practitioners should develop treatment plans or referral strategies (if onsite SUD treatment is unavailable) for patients who need SUD treatment.

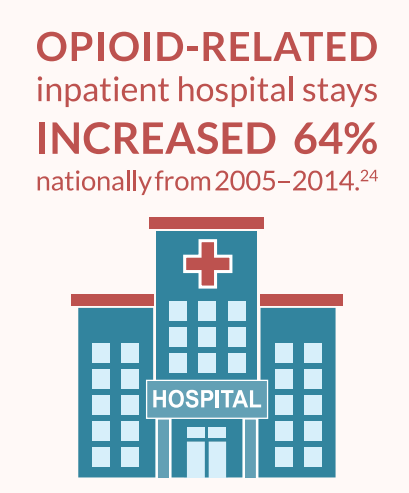
Part 3: Pharmacotherapy for Opioid Use Disorder

This part offers information and tools for healthcare professionals who prescribe, administer, or dispense OUD medications or treat other illnesses in patients who take these medications. It provides guidance on the use of buprenorphine, methadone, and naltrexone by healthcare professionals in:

- General medical settings, including hospitals.
- Office-based opioid treatment settings.
- Specialty addiction treatment programs, including OTPs.

In Part 3, readers will learn that:

- OUD medications are safe and effective when used appropriately.
- OUD medications can help patients reduce or stop illicit opioid use and improve their health and functioning.
- Pharmacotherapy should be considered for all patients with OUD. Opioid pharmacotherapies should be reserved for those with moderate-to-severe OUD with physical dependence.
- Patients with OUD should be informed of the risks and benefits of pharmacotherapy, treatment without medication, and no treatment.
- Patients should be advised on where and how to get treatment with OUD medication.



- Doses and schedules of pharmacotherapy must be individualized.

Part 4: Partnering Addiction Treatment Counselors With Clients and Healthcare Professionals

This part recommends ways that addiction treatment counselors can collaborate with healthcare professionals to support client-centered, trauma-informed OUD treatment and recovery. It also serves as a quick guide to medications that can treat OUD and presents strategies for clear communication with prescribers, creation of supportive environments for clients who take OUD medication, and ways to address other common counseling concerns when working with this population.

In Part 4, readers will learn that:

- Many patients taking OUD medication benefit from counseling as part of treatment.
- Counselors play the same role for clients with OUD who take medication as for clients with any other SUD.
- Counselors help clients recover by addressing the challenges and consequences of addiction.
- OUD is often a chronic illness requiring ongoing communication among patients and providers to ensure that patients fully benefit from both pharmacotherapy and psychosocial treatment and support.
- OUD medications are safe and effective when prescribed and taken appropriately.
- Medication is integral to recovery for many people with OUD. Medication usually produces better treatment outcomes than outpatient treatment without medication.
- Supportive counseling environments for clients who take OUD medication can promote treatment and help build recovery capital.

Part 5: Resources Related to Medications for Opioid Use Disorder

This part has a glossary and audience-segmented resource lists to help medical and behavioral health service providers better understand how to use OUD medications with their patients and to help patients better understand how OUD medications work. It is for all interested readers.

In Part 5, readers will learn that:

- Practice guidelines and decision-making tools can help healthcare professionals with OUD screening, assessment, diagnosis, treatment planning, and referral.
- Patient- and family-oriented resources provide information about opioid addiction in general; the role of medication, behavioral and supportive services, and mutual-help groups in the treatment of OUD; how-tos for identifying recovery support services; and how-tos for locating medical and behavioral health service providers who specialize in treating OUD or other SUDs.

Notes

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TIP Development Participants

Expert Panelists

Each Treatment Improvement Protocol's (TIP's) expert panel is a group of primarily nonfederal addiction-focused clinical, research, administrative, and recovery support experts with deep knowledge of the TIP's topic. With the Substance Abuse and Mental Health Services Administration's (SAMHSA's) Knowledge Application Program (KAP) team, they develop each TIP via a consensus-driven, collaborative process that blends evidence-based, best, and promising practices with the panel's expertise and combined wealth of experience.

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This TIP's scientific reviewers are among the foremost experts on the three medications discussed in this TIP to treat opioid use disorder. Their role in the collaborative TIP development process was to help the KAP team include current, accurate, and comprehensive information and instructions about the use of each of these medications.

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Field reviewers represent each TIP's intended target audiences. They work in addiction, mental health, primary care, and adjacent fields. Their direct front-line experience related to the TIP's topic allows them to provide valuable input on a TIP's relevance, utility, accuracy, and accessibility.

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Disclaimer

The views, opinions, and content expressed herein are the views of the consensus panel members and do not necessarily reflect the official position of SAMHSA or HHS. No official support of or endorsement by SAMHSA or HHS for these opinions or for the instruments or resources described is intended or should be inferred. The guidelines presented should not be considered substitutes for individualized client care and treatment decisions.

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TIP 63

MEDICATIONS FOR OPIOID USE DISORDER

Part 1: Introduction to Medications for Opioid Use Disorder Treatment

For Healthcare and Addiction Professionals, Policymakers, Patients, and Families

Part 1 of this **Treatment Improvement Protocol (TIP)** will help readers understand key facts and issues related to providing Food and Drug Administration (FDA)-approved medications used to treat opioid use disorder (OUD).

TIP Navigation

KEY MESSAGES

- Increasing opioid overdose deaths, illicit opioid use, and prescription opioid misuse constitute a public health crisis.
- OUD medications reduce illicit opioid use, retain people in treatment, and reduce risk of opioid overdose death better than treatment with placebo or no medication.
- Only physicians, nurse practitioners, and physician assistants can prescribe buprenorphine for OUD. They must get a federal waiver to do so.
- Only federally certified, accredited opioid treatment programs (OTPs) can dispense methadone to treat OUD. OTPs can administer and dispense buprenorphine without a federal waiver.
- Any prescriber can offer naltrexone.
- OUD medication can be taken on a short- or long-term basis, including as part of medically supervised withdrawal and as maintenance treatment.
- Patients taking medication for OUD are considered to be in recovery.
- Several barriers contribute to the underuse of medication for OUD.

SAMHSA
Substance Abuse and Mental Health Services Administration

PART 1: AN INTRODUCTION TO MEDICATIONS FOR THE TREATMENT OF OPIOID USE DISORDER

PART 1 of 5

Introduction to Medications for Opioid Use Disorder Treatment

Part 1 of this TIP offers a general introduction to providing medications to address opioid use disorder (OUD). It is for all audiences. Part 1 will help readers understand key facts and issues related to providing FDA-approved medications used to treat OUD. TIP Parts 2 through 5 cover these issues in more detail.

The Approach to OUD Care

According to the Substance Abuse and Mental Health Services Administration (SAMHSA) and the National Institute on Drug Abuse, addiction is a chronic, treatable illness. Opioid addiction, which generally corresponds with moderate to severe forms of OUD (Exhibit 1.1), often requires continuing care for effective treatment rather than an episodic, acute-care treatment approach.

The World Health Organization's (WHO's) principles of good care for chronic diseases can guide OUD care:[1]

- Develop a treatment partnership with patients.
- Focus on patients' concerns and priorities.
- Support patient self-management of illness.
- Use the five A's at every visit (assess, advise, agree, assist, and arrange).
- Organize proactive follow-up.
- Link patients to community resources/support.
- Work as a clinical team.
- Involve "expert patients," peer educators, and support staff in the health facility.
- Ensure continuity of care.

Chronic care management is effective for many long-term medical conditions, such as diabetes and cardiovascular disease, and it can offer similar benefits to patients with substance use disorders (SUDs); for example, it can help them stabilize, achieve remission of symptoms, and establish and maintain recovery. Good continuing care also provides, and links to, other medical, behavioral health, and community and recovery support services.

Estimated cost of the **OPIOID EPIDEMIC** was **$504 BILLION** in 2015.[2]

A noticeable theme in chronic disease management is patient-centered care. Patient-centered care empowers patients with information that helps them make better treatment decisions with the healthcare professionals involved in their care. Patients should receive information from their healthcare team that will help them understand OUD and the options for treating it, including treatment with FDA-approved medications. Healthcare professionals should also make patients aware of available, appropriate recovery support and behavioral health services.

EXHIBIT 1.1. Key Terms

Addiction: As defined by the American Society of Addiction Medicine, "a primary, chronic disease of brain reward, motivation, memory, and related circuitry."[3] It is characterized by inability to consistently abstain, impairment in behavioral control, craving, diminished recognition of significant problems with one's behaviors and interpersonal relationships, and a dysfunctional emotional response. Like other chronic diseases, addiction often involves cycles of **relapse** and **remission.** The *Diagnostic and Statistical Manual of Mental Disorders,* Fifth Edition[4] (DSM-5), does not use the term for diagnostic purposes, but it commonly describes the more severe forms of OUD.

Medically supervised withdrawal (formerly called detoxification): Using an opioid agonist (or an alpha-2 adrenergic agonist if an opioid agonist is not available) in tapering doses or other medications to help a patient discontinue illicit or prescription opioids.

Opioid misuse: The use of prescription opioids in any way other than as directed by a prescriber; the use of any opioid in a manner, situation, amount, or frequency that can cause harm to self or others.[5]

Opioid receptor agonist: A substance that has an affinity for and stimulates physiological activity at cell receptors in the central nervous system (CNS) that are normally stimulated by opioids. Mu-opioid receptor full agonists (e.g., methadone) bind to the mu-opioid receptor and produce actions similar to those produced by the endogenous opioid beta-endorphin. Increasing the dose increases the effect. Mu-opioid receptor partial agonists (e.g., buprenorphine) bind to the mu-opioid receptor. Unlike with full agonists, increasing their dose may not produce additional effects once they have reached their maximal effect. At low doses, partial agonists may produce effects similar to those of full agonists.

Opioid receptor antagonist: A substance that has affinity for opioid receptors in the CNS without producing the physiological effects of opioid agonists. Mu-opioid receptor antagonists (e.g., naltrexone) can block the effects of exogenously administered opioids.

Opioids: All natural, synthetic, and semisynthetic substances that have effects similar to morphine. They can be used as medications having such effects (e.g., methadone, buprenorphine, oxycodone).

Opioid treatment program (OTP): An accredited treatment program with SAMHSA certification and Drug Enforcement Administration registration to administer and dispense opioid agonist medications that are approved by FDA to treat opioid addiction. Currently, these include methadone and buprenorphine products. Other pharmacotherapies, such as naltrexone, may be provided but are not subject to these regulations. OTPs must provide adequate medical, counseling, vocational, educational, and other assessment and treatment services either onsite or by referral to an outside agency or practitioner through a formal agreement.[6]

Opioid use disorder (OUD): Per DSM-5, a disorder characterized by loss of control of opioid use, risky opioid use, impaired social functioning, tolerance, and withdrawal. Tolerance and withdrawal do not count toward the diagnosis in people experiencing these symptoms when using opioids under appropriate medical supervision. OUD covers a range of severity and replaces what DSM-IV termed "opioid abuse" and "opioid dependence." An OUD diagnosis is applicable to a person who uses opioids and experiences at least 2 of the 11 symptoms in a 12-month period. (See Exhibit 2.13 in Part 2 for full DSM-5 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. Even individuals with severe and chronic SUDs can, with help, overcome their SUDs and regain health and social function. Although abstinence from all substance misuse is a cardinal feature of a recovery lifestyle, it is not the only healthy, prosocial feature. Patients taking FDA-approved medication to treat OUD can be considered in recovery.

Relapse: A process in which a person with OUD who has been in **remission** experiences a return of symptoms or loss of remission. A relapse is different from a **return to opioid use** in that it involves more than a single incident of use. Relapses occur over a period of time and can be interrupted. Relapse need not be long lasting. The TIP uses relapse to describe relapse prevention, a common treatment modality.

Remission: A medical term meaning a disappearance of signs and symptoms of the disease.[7] DSM-5 defines remission as present in people who previously met OUD criteria but no longer meet any OUD criteria (with the possible exception of craving).[8] Remission is an essential element of **recovery.**

Return to opioid use: One or more instances of **opioid misuse** without a return of symptoms of OUD. A return to opioid use may lead to **relapse.**

As is true for patients undergoing treatment for any chronic medical condition, patients with OUD should have access to medical, mental health, addiction counseling, and recovery support services that they may need to supplement treatment with medication. Medical care should include preventive services and disease management. Patients with OUD who have mental disorders should have access to mental health services.

Treatment and support services should reflect each patient's individual needs and preferences. Some patients, particularly those with co-occurring disorders, may require these treatments and services to achieve sustained remission and recovery.

The words you use to describe both OUD and an individual with OUD are powerful and can reinforce prejudice, negative attitudes, and discrimination. Negative attitudes held by the public and healthcare professionals can deter people from seeking treatment, make patients leave treatment prematurely, and contribute to worse treatment outcomes. The TIP expert panel recommends that providers always use medical terms when discussing SUDs (e.g., positive or negative urine sample, not dirty or clean sample) and use person-first language (e.g., a person with an SUD, not a user, alcoholic, or addict). Exhibit 1.1 defines some key terms. A full glossary is in Part 5 of this TIP.

RESOURCE ALERT

Shared Decision Making

SAMHSA's shared decision-making tool is helpful for educating patients and their families about OUD. The information this tool provides can help patients make informed decisions about their care (http://archive.samhsa.gov/MAT-Decisions-in-Recovery/Default.aspx).

Overview of Medications for OUD

There is no "one size fits all" approach to OUD treatment. Many people with OUD benefit from treatment with medication for varying lengths of time, including lifelong treatment. Ongoing outpatient medication treatment for OUD is linked to better retention and outcomes than treatment without medication. Even so, some people stop using opioids on their own; others recover through support groups or specialty outpatient or residential treatment with or without medication. Still, FDA-approved medication should be considered and offered to patients with OUD as part of their treatment.

Benefits

The three FDA-approved medications used to treat OUD improve patients' health and wellness by:

- Reducing or eliminating withdrawal symptoms: methadone, buprenorphine.
- Blunting or blocking the effects of illicit opioids: methadone, naltrexone, buprenorphine.
- Reducing or eliminating cravings to use opioids: methadone, naltrexone, buprenorphine.

See Exhibit 1.2 for further comparison between these medications.

Effectiveness

The science demonstrating the effectiveness of medication for OUD is strong. For example, methadone, extended-release injectable naltrexone (XR-NTX), and buprenorphine were each found to be more effective in reducing illicit opioid use than no medication in randomized clinical trials,[9,10,11,12] which are the gold standard for demonstrating efficacy in clinical medicine. Methadone and buprenorphine treatment have also been associated with reduced risk of overdose death.[13,14,15,16,17]

EXHIBIT 1.2. Comparison of Medications for OUD

PRESCRIBING CONSIDERATIONS	METHADONE	NALTREXONE	BUPRENORPHINE
Mechanism of Action at mu-Opioid Receptor	Agonist	Antagonist	Partial agonist
Phase of Treatment	Medically supervised withdrawal, maintenance	Prevention of relapse to opioid dependence, following medically supervised withdrawal	Medically supervised withdrawal, maintenance
Route of Administration	Oral	Oral, intramuscular extended-release	Sublingual, buccal, subdermal implant, subcutaneous extended release
Possible Adverse Effects	Constipation, hyperhidrosis, respiratory depression, sedation, QT prolongation, sexual dysfunction, severe hypotension including orthostatic hypotension and syncope, misuse potential, neonatal abstinence syndrome	Nausea, anxiety, insomnia, precipitated opioid withdrawal, hepatotoxicity, vulnerability to opioid overdose, depression, suicidality, muscle cramps, dizziness or syncope, somnolence or sedation, anorexia, decreased appetite or other appetite disorders **Intramuscular:** Pain, swelling, induration (including some cases requiring surgical intervention)	Constipation, nausea, precipitated opioid withdrawal, excessive sweating, insomnia, pain, peripheral edema, respiratory depression (particularly combined with benzodiazepines or other CNS depressants), misuse potential, neonatal abstinence syndrome **Implant:** Nerve damage during insertion/removal, accidental overdose or misuse if extruded, local migration or protrusion **Subcutaneous:** Injection site itching or pain, death from intravenous injection
Regulations and Availability	Schedule II; only available at federally certified OTPs and the acute inpatient hospital setting for OUD treatment	Not a scheduled medication; not included in OTP regulations; requires prescription; office-based treatment or specialty substance use treatment programs, including OTPs	Schedule III; requires waiver to prescribe outside OTPs **Implant:** Prescribers must be certified in the Probuphine Risk Evaluation and Mitigation Strategy (REMS) Program. Providers who wish to insert/remove implants are required to obtain special training and certification in the REMS Program **Subcutaneous:** Healthcare settings and pharmacies must be certified in the Sublocade REMS Program and only dispense the medication directly to a provider for administration

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This doesn't mean that remission and recovery occur only through medication. Some people achieve remission without OUD medication, just as some people can manage type 2 diabetes with exercise and diet alone. But just as it is inadvisable to deny people with diabetes the medication they need to help manage their illness, it is also not sound medical practice to deny people with OUD access to FDA-approved medications for their illness.

Medication for OUD should be successfully integrated with outpatient and residential treatment. Some patients may benefit from different levels of care during the course of their lives. These different levels include outpatient counseling, intensive outpatient treatment, inpatient treatment, or long-term therapeutic communities. Patients receiving treatment in these settings should have access to FDA-approved medications for OUD.

Patients treated with OUD medications can benefit from individualized psychosocial supports. These can be offered by patients' healthcare providers in the form of medication management and supportive counseling and/or by other providers offering adjunctive addiction counseling, contingency management, recovery coaching, mental health services, and other services (e.g., housing supports) that particular patients may need.

> **The TIP expert panel strongly recommends informing all patients with OUD about the risks and benefits of treatment of OUD with all FDA-approved medications. Alternatives to these treatments and their risks and benefits should be discussed. Patients should receive access to such medications if clinically appropriate and desired by the patients.**

Expanding access to FDA-approved medications is an important public health strategy.[19] A substantial gap exists between the number of people needing OUD treatment and the capacity to treat those individuals with OUD medication. In 2012, the gap was estimated at nearly 1 million people, with approximately 80 percent of OTPs nationally operating at 80 percent capacity or greater.[20] Blue Cross Blue Shield reported a 493 percent increase in members diagnosed with OUD from 2010 to 2016 but only a 65 percent increase in the use of medication for OUD.[21] **Improving access is crucial to closing the wide gap between the need for treatment with OUD medications and the availability of such treatment,** given the strong evidence of OUD medications' effectiveness.[22]

Methadone

Methadone retains patients in treatment and reduces illicit opioid use more effectively than placebo, medically supervised withdrawal, or no treatment, as numerous clinical trials and meta-analyses of studies conducted in many countries show.[23,24,25] Higher methadone doses are associated with superior outcomes.[26,27] Given the evidence of methadone's effectiveness, WHO lists it as an essential medication.[28]

Methadone treatment has by far the largest, oldest evidence base of all treatment approaches to opioid addiction. Large multisite longitudinal studies from the world over support methadone maintenance's effectiveness.[29,30,31] Longitudinal studies have also found that it is associated with:[32,33,34,35,36,37,38,39,40]

- Reduced risk of overdose-related deaths.
- Reduced risk of HIV and hepatitis C infection.
- Lower rates of cellulitis.
- Lower rates of HIV risk behavior.
- Reduced criminal behavior.

Naltrexone

XR-NTX reduces illicit opioid use and retains patients in treatment more effectively than placebo and no medication, according to findings from randomized controlled trials.[41,42,43]

In a two-group random assignment study of adults who were opioid dependent and involved in the justice system, all participants received brief counseling and community treatment referrals. One group received no medication, and the other group received XR-NTX. During the 6-month follow-up period, compared with the no-medication group, the group that received the medication demonstrated:[44]

- Longer time to return to substance use (10.5 weeks versus 5.0 weeks).
- A lower rate of return to use (43 percent versus 64 percent).
- A higher percentage of negative urine screens (74 percent versus 56 percent).

There are two studies comparing XR-NTX to sublingual buprenorphine. A multisite randomized trial assigned adult residential treatment patients with OUD to either XR-NTX or buprenorphine. Patients randomly assigned to buprenorphine had significantly lower relapse rates during 24 weeks of outpatient treatment than patients assigned to XR-NTX.[45] This finding resulted from challenges in completing XR-NTX induction, such that a significant proportion of patients did not actually receive XR-NTX. However, when comparing only those participants who started their assigned medication, no significant between-group differences in relapse rates were observed. Because dose induction was conducted with inpatients, findings may not be generalizable to dose induction in outpatient settings, where most patients initiate treatment. A 12-week trial among adults with opioid dependence in Norway who were opioid abstinent at the time of random assignment found that XR-NTX was as effective as buprenorphine in retaining patients in treatment and in reducing illicit opioid use.[46]

Oral naltrexone is also available, but it has not been found to be superior to placebo or to no medication in clinical trials.[47] Nonadherence limits its use.

Buprenorphine

Buprenorphine in its sublingual form retains patients in treatment and reduces illicit opioid use more effectively than placebo.[48] It also reduces HIV risk behaviors.[49,50] A multisite randomized trial with individuals addicted to prescription opioids showed that continued buprenorphine was superior to buprenorphine dose taper in reducing illicit opioid use.[51] Another randomized trial showed that continued buprenorphine also improved treatment retention and reduced illicit prescription opioid use compared with buprenorphine dose taper.[52] Long-term studies of buprenorphine show its effectiveness outside of clinical research protocols.[53,54] Naloxone, a short-acting opioid antagonist, is also often included in the buprenorphine formulation to help prevent diversion to injected misuse. Because of the evidence of buprenorphine's effectiveness, WHO lists it as an essential medication.[55] Buprenorphine is available in "transmucosal" (i.e., sublingual or buccal) formulations.

Buprenorphine implants can be effective in stable patients. FDA approved implants (Probuphine) after a clinical trial showed them to be as effective as relatively low-dose (i.e., 8 mg or less daily) sublingual buprenorphine/naloxone (Suboxone) for patients who are already clinically stable.[56] More research is needed to establish implants' effectiveness outside of research studies, but findings to date are promising.[57,58]

FDA approved buprenorphine extended-release injection (Sublocade) in November 2017 to treat patients with moderate or severe OUD who have first received treatment with transmucosal buprenorphine for at least 1 week. This buprenorphine formulation is a monthly subcutaneous injection.

Exhibit 1.2 compares medications for OUD.

Cost Effectiveness and Cost Benefits

Cost-effectiveness and cost-benefit analyses can further our understanding of OUD medications' effectiveness.

Data indicate that medications for OUD are cost effective. Cost-effectiveness analyses compare the cost of different treatments with their associated outcomes (e.g., negative opioid urine tests). Such analyses have found that:

- Methadone and buprenorphine are more cost effective than OUD treatment without medication.[59]
- Counseling plus buprenorphine leads to significantly lower healthcare costs than little or no treatment among commercially insured patients with OUD.[60]
- Treatment with any of the three OUD medications this TIP covers led to lower healthcare usage and costs than treatment without medication in a study conducted in a large health plan.[61]

Relatively few cost-benefit analyses have examined addiction treatment with medication separately from addiction treatment in general.[62] Cost-benefit studies compare a treatment's cost with its benefits. The treatment is cost beneficial if its benefits outweigh its cost. These benefits can include:

- Reduced expenditures because of decreased crime.
- Reduced expenditures related to decreases in the use of the justice system.
- Improved quality of life.
- Reduced healthcare spending.
- Greater earned income.

Methadone treatment in OTPs can reduce justice system and healthcare costs.[63,64]

Requirements and Regulations

Following is a summary of regulations and requirements that apply to the three OUD medications. Part 3 of this TIP discusses the pharmacology and dosing of these medications.

Only federally certified and accredited OTPs can dispense methadone for the treatment of OUD. Methadone is typically given orally as a liquid.[65]

OTPs can dispense buprenorphine under OTP regulations without using a federal waiver.

Individual healthcare practitioners can prescribe buprenorphine in any medical setting, as long as they apply for and receive waivers of the special registration requirements defined in the Controlled Substances Act by meeting the requirements of the Drug Addiction Treatment Act of 2000 (DATA 2000) and the revised Comprehensive Addiction and Recovery Act. Physicians can learn how to obtain a waiver online (www.samhsa.gov/medication-assisted-treatment/buprenorphine-waiver-management/qualify-for-physician-waiver), as can nurse practitioners and physician assistants (www.samhsa.gov/medication-assisted-treatment/qualify-nps-pas-waivers).

- Eligible physicians, nurse practitioners, and physician assistants can treat up to 30 patients at one time in the first year of practice.
- They can apply to increase this number to 100 patients in the second year.
- After a year at the 100-patient limit, **only** physicians may apply to increase to up to 275 patients (with additional practice and reporting requirements).

Prescribing buprenorphine implants requires Probuphine REMS Program certification. Providers who wish to insert or remove implants must obtain live training and certification in the REMS Program.

Healthcare settings and pharmacies must get Sublocade REMS Program certification to dispense this medication and can only dispense it directly to healthcare providers for subcutaneous administration.

Naltrexone has no regulations beyond those that apply to any prescription pharmaceutical. Any healthcare provider with prescribing

authority, including those practicing in OTPs, can prescribe its oral formulation and administer its long-acting injectable formulation.

The Controlled Substances Act contains a few exceptions from the requirement to provide methadone through an OTP or buprenorphine through an OTP or a waivered practitioner. These include (1) administering (not prescribing) an opioid for no more than 3 days to a patient in acute opioid withdrawal while preparations are made for ongoing care and (2) administering opioid medications in a hospital to maintain or detoxify a patient as an "incidental adjunct to medical or surgical treatment of conditions other than addiction."[66]

Duration of Treatment With OUD Medication

Patients can take medication for OUD on a short-term or long-term basis. However, patients who discontinue OUD medication generally return to illicit opioid use. Why is this so, even when discontinuation occurs slowly and carefully? Because the more severe form of OUD (i.e., addiction) is more than physical dependence. Addiction changes the reward circuitry of the brain, affecting cognition, emotions, and behavior. Providers and their patients should base decisions about discontinuing OUD medication on knowledge of the evidence base for the use of these medications, individualized assessments, and an individualized treatment plan they collaboratively develop and agree upon. Arbitrary time limits on the duration of treatment with OUD medication are inadvisable.

Maintenance Treatment

The best results occur when a patient receives medication for as long as it provides a benefit. This approach is often called "maintenance treatment."[67,68] Once stabilized on OUD medication, many patients stop using illicit opioids completely. Others continue to use for some time, but less frequently and in smaller amounts, which reduces their risk of morbidity and overdose death.

OUD medication gives people the time and ability to make necessary life changes associated with long-term remission and recovery (e.g., changing the people, places, and things connected with their drug use), and to do so more safely. Maintenance treatment also minimizes cravings and withdrawal symptoms. And it lets people better manage other aspects of their life, such as parenting, attending school, or working.

Medication Taper

After some time, patients may want to stop opioid agonist therapy for OUD through gradually tapering doses of the medication. Their outcomes will vary based on factors such as the length of their treatment, abstinence from illicit drugs, financial and social stability, and motivation to discontinue medication.[69] Longitudinal studies show that most patients who try to stop methadone treatment relapse during or after completing the taper.[70,71] For example, in a large, population-based retrospective study, only 13 percent of patients who tapered

RESOURCE ALERT

OUD Medication Treatment Limits and Reporting Requirements

The following websites provide information about (1) the Department of Health and Human Services final rule to increase patient access to medication for OUD and (2) associated reporting requirements:

www.federalregister.gov/documents/2016/07/08/2016-16120/medication-assisted-treatment-for-opioid-use-disorders

www.samhsa.gov/sites/default/files/programs_campaigns/medication_assisted/understanding-patient-limit275.pdf

from methadone had successful outcomes (no treatment reentry, death, or opioid-related hospitalization within 18 months after taper).[72] A clinical trial of XR-NTX versus treatment without medication also found increased risk of returning to illicit opioid use after discontinuing medication.[73]

Adding psychosocial treatments to taper regimens may not significantly improve outcomes compared with remaining on medication. One study randomly assigned participants to methadone maintenance or to 6 months of methadone treatment with a dose taper plus intensive psychosocial treatment. The maintenance group had more days in treatment and lower rates of heroin use and HIV risk behavior at 12-month follow-up.[74] Patients wishing to taper their opioid agonist medication should be offered psychosocial and recovery support services. They should be monitored during and after dose taper, offered XR-NTX, and encouraged to resume treatment with medication quickly if they return to opioid use.

Medically Supervised Withdrawal

Medically supervised withdrawal is a process in which providers offer methadone or buprenorphine on a short-term basis to reduce physical withdrawal signs and symptoms. Formerly called detoxification, this process gradually decreases the dose until the medication is discontinued, typically over a period of days or weeks. Studies show that most patients with OUD who undergo medically supervised withdrawal will start using opioids again and won't continue in recommended care.[75,76,77,78,79,80,81,82,83] Psychosocial treatment strategies, such as contingency management, can reduce dropout from medically supervised withdrawal, opioid use during withdrawal, and opioid use following completion of withdrawal.[84] Medically supervised withdrawal is necessary for patients starting naltrexone, which requires at least 7 days without short-acting opioids and 10 to 14 days without long-acting opioids.

Patients who complete medically supervised withdrawal are at risk of opioid overdose.

> **Primary care physicians are on the front lines of providing office-based treatment with medication for OUD.**

Treatment Settings

Almost all healthcare settings are appropriate for screening and assessing for OUD and offering medication onsite or by referral. Settings that offer OUD treatment have expanded from specialty sites (certified OTPs, residential facilities, outpatient addiction treatment programs, and addiction specialist physicians' offices) to general primary care practices, health centers, emergency departments, inpatient medical and psychiatric units, jails and prisons, and other settings.

OUD medications should be available to patients across all settings and at all levels of care—as a tool for remission and recovery. Because of the strength of the science, a 2016 report from the Surgeon General[85] urged adoption of medication for OUD along with recovery supports and other behavioral health services throughout the healthcare system.

Challenges to Expanding Access to OUD Medication

Despite the urgent need for treatment throughout the United States, only about 21.5 percent of people with OUD received treatment from 2009 to 2013.[86] The Centers for Disease Control and Prevention lists more than 200 U.S. counties as at risk for an HIV or a hepatitis C virus outbreak related to injection drug use.[87]

> **Sustained public health efforts are essential to address the urgent need for OUD treatment and the risk of related overdose, HIV, and hepatitis C virus epidemics. These efforts must remove barriers and increase access to OUD medication.**

Resources

Patient success stories are inspirational. They highlight the power of OUD medication to help people achieve remission and recovery. See the "Patient Success Stories" section in Part 5 of this TIP.

Part 5 of this TIP also contains community resources and advocacy resources. The community resources are for OTP, addiction treatment, and office-based providers The advocacy resources can help patients and others advocate for OUD medication for themselves and in their communities.

Notes

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