Management of opioid use disorder across the care continuum

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These are general recommendations only; specific clinical decisions should be made by the treating clinician based on an individual patient's clinical condition.

Management of opioid use disorder across the care continuum

Activity Start Date: December 16, 2024
Activity Termination Date: December 15, 2027

This activity offers CE credit for:

1. Medicine (AMA)
2. Nurses (ANCC)
3. Pharmacy (ACPE)
4. Other

All other attendees will receive a Certificate of Attendance

Activity Overview:

The primary goals of this educational program are to address the need for effective treatment of patients with Opioid Use Disorder (OUD) in the acute and primary care settings, to educate clinicians about the diagnosis and evidence-based treatment of OUD with medications, and to encourage clinicians to prescribe buprenorphine for patients with OUD.

The education program has several components, which include:

1. The written evidence report (print monograph)
2. Summary document of top 4-5 key messages
3. "Academic detailing" educational sessions in physicians' offices with trained outreach educators (pharmacists, nurses, physicians) who present the material interactively
4. Reference cards for easy access to key materials
5. Patient education brochure

This program works to synthesize the current clinical information on this topic into accessible, non-commercial, evidence-based educational material, which is taught interactively to providers by specially trained clinical educators.

Learning Objectives:

After completing this activity, participants will be able to:

- Identify patients with suspected opioid use disorder (OUD) and initiate treatment using SBIRT: Screening, Brief Intervention, and Referral to Treatment
- Use the *DSM-5-TR* diagnostic criteria to diagnose OUD
- Describe the three FDA-approved medications for treating OUD
- Explain the pharmacologic differences between the three medications used for OUD and the differing contexts in which they are administered/prescribed
- Plan to initiate buprenorphine treatment in appropriate patients
- Implement overdose prevention and harm reduction strategies

Financial Support:

There is no commercial support associated with this activity.

Target Audience:

The educational program is designed for physicians, including general internal medicine doctors, family practice physicians, emergency department physicians, nurse practitioners, physician assistants, pharmacists, nurses, and all other clinicians caring for patients who have or are at risk for opioid use disorder (OUD).

Credit Information:

In support of improving patient care, this activity has been planned and implemented by CME Outfitters, LLC and Alosa Health. CME Outfitters, LLC is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

Physicians: CME Outfitters, LLC, designates this enduring activity for a maximum of **1.25** *AMA PRA Category 1 Credit(s)™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Note to Osteopathic Physicians: The AOA automatically recognizes *AMA PRA Category 1 Credit* ™ as AOA Category 2 credit.

Nurses: This activity is designated for **1.25** nursing contact hours.

Note to Nurse Practitioners: Nurse practitioners can apply for *AMA PRA Category 1 Credit™* through the American Academy of Nurse Practitioners (AANP). AANP will accept *AMA PRA Category 1 Credit™* from Jointly Accredited Organizations. Nurse practitioners can also apply for credit through their state boards. The content of this CNE activity pertains to Pharmacology.

California Residents: This continuing nursing education activity was approved by the California Board of Registered Nursing. CME Outfitters LLC's provider number is CEP15510.

Pharmacists: This (application-based or knowledge-based) activity is approved for **1.25** contact hours (0.0125 CEUs) of continuing pharmacy credit UAN JA 0007185-9999-24-111-H08-P

Disclosure Declaration

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Disclosures:

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Scott J. Hershman, MD, FACEHP, CHCP is the Senior Director, Accreditation & Joint Providership at CME Outfitters. Dr. Hershman has nothing to disclose.

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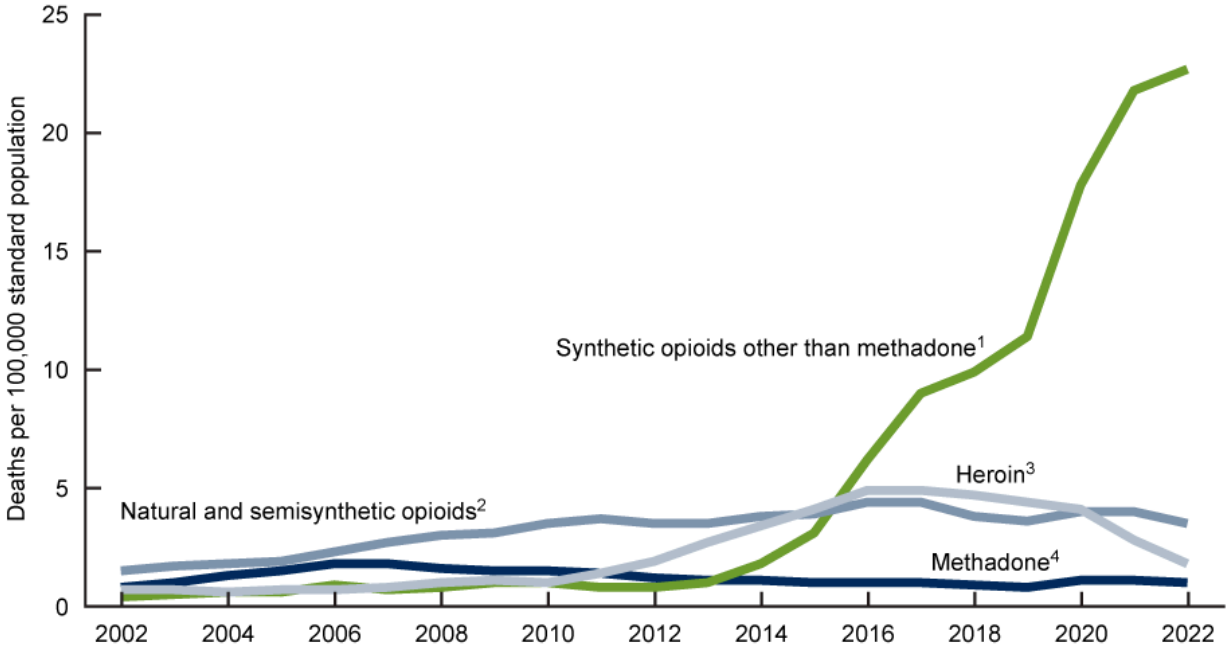
Table of Contents

The opioid overdose epidemic

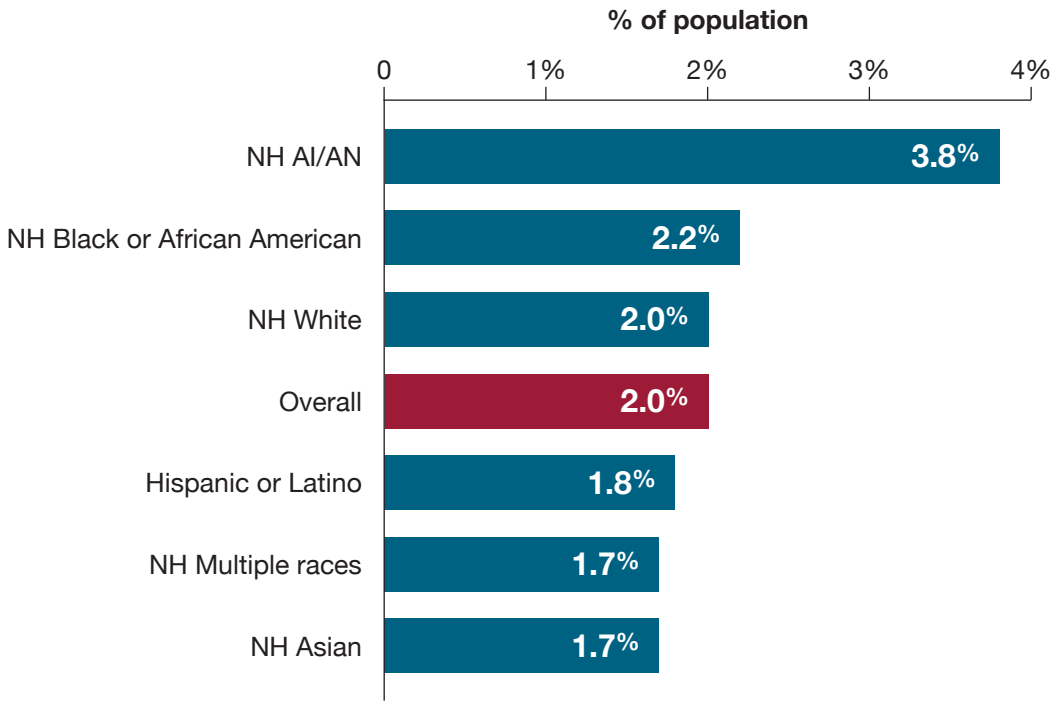
The U.S. has seen three successive waves of opioid use and associated overdose deaths.[1] The first wave began in the 1990s and was due to steadily rising rates of opioid analgesic prescribing. In 2010, the second wave began, characterized by sharply increasing deaths from heroin use that reached "epidemic" levels in 2011 as described by the Centers for Disease Control and Prevention (CDC).[2] The third wave began in 2013 with a rise in overdose deaths attributed to synthetic opioids, particularly those involving illicitly-manufactured fentanyl. In 2022, the CDC estimated that 81,806 people in the U.S. died from opioid overdoses, which was more than in any previous year.[3] These overdose deaths often affect young and otherwise healthy individuals; in 2019 and 2020 people aged 35-44 years had the highest absolute number of overdose deaths.[4]

Figure 1: Opioid-related overdose deaths by opioid type in the U.S.[5]



American Indian or Alaska Native (AI/AN) communities have been particularly impacted by the ongoing epidemic of opioid use disorder (OUD) and opioid-related overdoses and death. The AI/AN population was estimated in the 2020 census as 9.7 million,[6] with 574 tribes currently recognized by the U.S. Bureau of Indian Affairs.[7] Among people aged 18 or older in 2022 (the latest year for which these data are available) the percentage who had a past year OUD was 7.6% among AI/AN people compared to 2.1% for White people, 3.2% for Black or African American people, and 1.3% for Asian people.[8] Similarly, rates of prescription pain reliever use disorder were highest among AI/AN people (3.9%) compared to other races/ethnicities.[9]

Figure 2: Opioid use disorder in adults age 12 and older by origin and race in 2023[10]



NH=Not Hispanic; AI/AN=American Indian/Alaska Native

These statistics occur against the backdrop of the wider crisis of opioid misuse and abuse. The Centers for Disease Control and Prevention estimated that in the 12 months ending in December, 2022, 105,452 people in the U.S. died from an opioid overdose, equating to 288 overdose deaths each day.[11]

Key opioid-related terms

Opioid: any psychoactive chemical resembling morphine and binding to morphine/endorphin receptors in the brain.

Opiate: "natural" opioids derived from the opium poppy (e.g., opium, morphine, codeine).

Semi-synthetic opioid: an analgesic containing both natural and manufactured compounds (e.g., oxycodone, hydrocodone, hydromorphone, oxymorphone).

Synthetic opioid: a fully-human-made compound (e.g., methadone, tramadol, and fentanyl).

These alarming statistics persist despite strong evidence that treatment with medications for OUD (MOUD) delivered by primary care clinicians or in specialized clinics can significantly reduce rates of death, overdose, and return to use in persons with OUD.[12,13] These evidence-based treatments, however, remain significantly under-used. Only about 22% of the 2.5 million people with OUD in the U.S. received MOUD treatment in 2021.[9] Access to MOUD treatment, as well as many other services for those with

substance use disorders, can be limited by a range of factors such as high levels of poverty, lower levels of education, higher rates of trauma, and higher-than-average rates of certain physical problems such as diabetes and cardiovascular disease – as well as limitations of the health-care system.

This report summarizes current best practices for managing patients with OUD and presents the evidence supporting the use of MOUD.[14]

BOTTOM LINE: Opioid misuse is a serious problem in the U.S., claiming approximately 288 lives every day from overdoses.

What is opioid use disorder?

OUD is a chronic, often-relapsing, but treatable brain disease resulting from neuroadaptation to repeated opioid use on brain structure and function that causes significant negative personal, economic, and social consequences. Previously, OUD was termed **"**opioid abuse," "opioid dependence," or **"**opioid addiction," but in this evidence document we use "opioid use disorder" because this is the term used in the latest edition of the *Diagnostic and Statistical Manual of Mental Disorders (5th Edition, Text Revision [DSM-5-TR])*. The changes in neurocircuitry involved in the development of substance use disorders is well-described[15,16] and understanding these changes helps explain why persons with OUD can become trapped in addiction and may be unable to stop opioid use without assistance.

Rates of OUD diagnoses have increased 4-5 fold in recent years, according to market research and insurance claims data.[17-19] Rates of opioid misuse have risen as well, with misuse defined as taking opioids for reasons other than prescribed or in amounts greater than prescribed, or using opioids in ways intended to enhance their potency, such as intranasal and injection use. Many people with OUD or who misuse opioids obtain the substances via a valid prescription (43.2%) or from friends and relatives (44.9%).[9] Both OUD and opioid misuse are associated with intentional and unintentional opioid-related overdoses.[20]

According to *DSM-5-TR,* OUD is diagnosed based on clinical evaluation and a determination that a patient has problematic opioid use leading to clinically significant impairment or distress involving at least two of the following criteria within a 12-month period:[21]

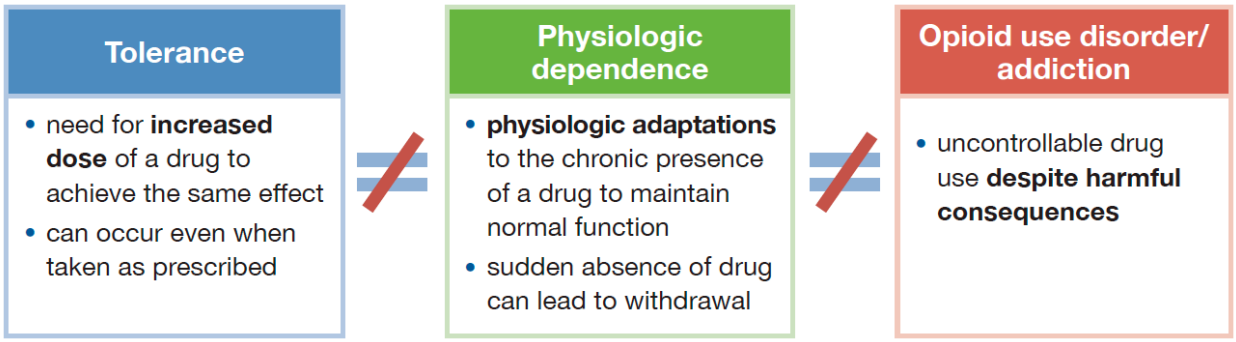
- opioids taken in larger amounts, or for longer periods, than intended
- unsuccessful attempts to control or reduce use
- significant time lost obtaining, consuming, and recovering from opioids
- craving or a strong desire or urge to use opioids
- failure to complete obligations (i.e., work, home, or school) due to opioids
- persistent or recurrent social or interpersonal problems due to opioids
- giving up enjoyable social, work, or recreational activities due to opioids
- recurrent opioid use in hazardous situations (e.g., driving)
- continued use despite a physical or psychological problem caused by or worsened by opioid use
- tolerance (unless opioids are being taken as prescribed)
- using opioids to prevent withdrawal symptoms (unless opioids are being taken as prescribed)

The severity of OUD exists on a continuum and can be characterized by the number of *DSM-5-TR* criteria the patient meets:

- mild OUD (2-3 criteria)
- moderate OUD (4-5 criteria)
- severe OUD (≥ 6 criteria)

It's important to differentiate OUD, as defined above, with opioid dependence. Physiological dependence refers to the normal physiologic adaptation that occurs in the chronic presence of a drug or substance. Many drugs cause dependence but not addiction, such as selective serotonin reuptake inhibitors (SSRIs) and the antihypertensive clonidine. However, when people withdraw from these medications, they do not crave them and once successfully tapered, they do not have recurrent use. By contrast, opioid use disorder involves cravings, lack of control, and recurrent use despite harm. Additionally, physiological dependence to a medication in order to function is not pathological. For example, many people require a daily medication to treat a chronic condition, such as insulin for blood sugar maintenance. The conflation of opioid dependence with OUD can stigmatize the medications used to treat OUD such as buprenorphine, because these medications can very successfully reduce or eliminate the core symptoms of OUD (e.g., cravings, lack of control, and using despite harmful consequences).

Figure 3: Opioid dependence does not equal opioid use disorder[22]



BOTTOM LINE: OUD is a problematic pattern of opioid use that causes significant impairment or distress, can be diagnosed using *DSM-5-TR* criteria, and is categorized as mild, moderate, or severe based on the number of criteria the patient meets. OUD is not the same as opioid dependence.

Screening for opioid misuse and OUD

Screening, Brief Intervention, and Referral to Treatment (SBIRT) is an evidence-based framework screening patients for OUD.[23] SBIRT typically takes 5-10 minutes to administer and has been endorsed by the Substance Abuse and Mental Health Services Administration (SAMHSA).[24]

SAMHSA recommends universal screening for substance use disorders, which includes OUD, with approaches such as SBIRT, because of the high prevalence of these disorders in patients visiting primary care settings. However, universal screening for OUD with urine, blood, or oral fluid tests is *not* recommended in primary care.[24]

Universal screening can be as simple as asking a single question, such as "*How many times in the past year have you used an illegal drug or used a prescription medication for nonmedical reasons?"* Patients who respond "none" may benefit from affirmation of healthy behaviors. Those patients reporting any use require further discussion to understand which substances are being used and what the patterns of use are. This can be done with an informal conversation or formal screening tools.

More comprehensive SUD screening tools include:

- Drug Abuse Screening Test (DAST)-10
- Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST)
- Tobacco, Alcohol, Prescription medication, and other Substance use (TAPS)[25]
- the CAGE questionnaire adapted to include drugs (CAGE-AID)[25]

If results from an assessment tool indicate that a patient has misused opioids, probe further and proceed using the SBIRT approach and integrating five key clinical steps summarized as **the "5 A's"**:

- ***Ask*** about opioid use.
- ***Assess*** the patient for OUD using *DSM-5-TR* criteria and, if a diagnosis is appropriate, assess their goals regarding treatment.
- ***Advise*** patients to use medication-based treatment with, or without, psychotherapeutic or cognitive-behavioral treatments.
- ***Assist*** patients by connecting them with treatment
  - provide a referral if not available in-office
  - recommend free, peer-facilitated mutual support groups such as Narcotics Anonymous, Alcoholics Anonymous, and Self-Management And Recovery Training (SMART Recovery),
  - educate patients about overdose prevention, and
  - prescribe or otherwise provide an opioid reversal medication (e.g., naloxone).
- ***Arrange*** follow-up appointments, either in person or by telehealth.

Motivational interviewing techniques

Motivational interviewing (MI) is a strategic conversational approach that can be used in the context of many problematic patient behaviors, including substance use disorders. It can be used at several steps in the SBIRT framework described above, particularly in the Ask and Assess phases. Research has demonstrated that MI can effectively help patients raise awareness of their own values and goals while supporting their commitment to changing their behaviors related to opioids or other substances.[26] A systematic review and meta-analysis of 59 studies including 12,342 patients with SUDs found that, compared to control treatments, patients receiving MI reduced their use of substances significantly more than those in control groups, although the effect of the MI interventions declined with longer follow-up periods.[27]

The core skills involved in using MI are described with the OARS acronym:[26]

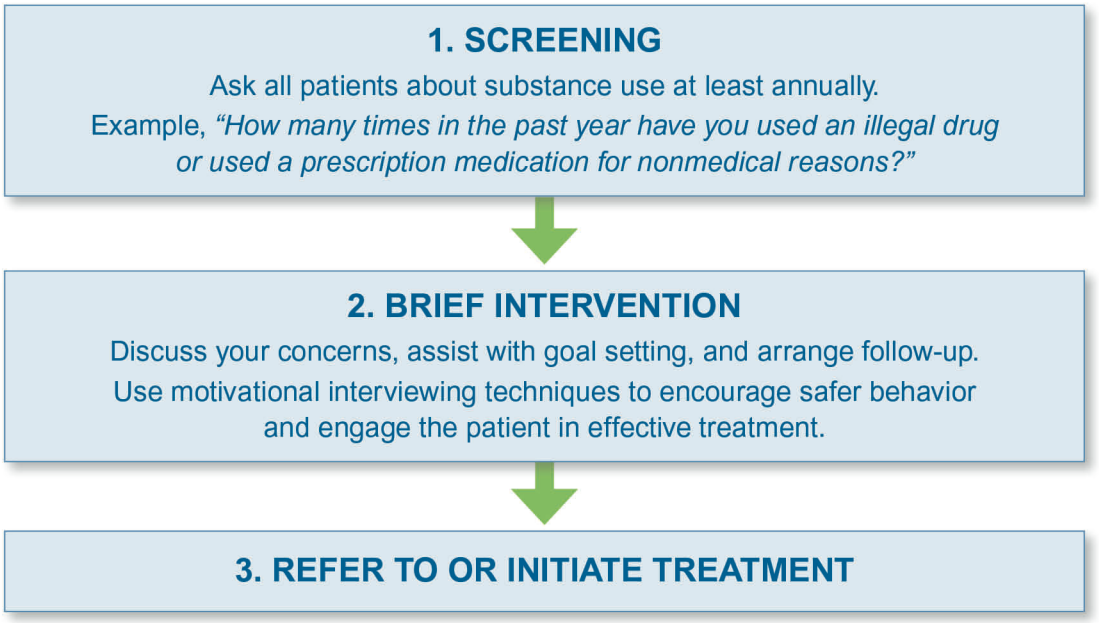
- Clinicians should use **open questions** to elicit information and stories from patients and to gain a fuller understanding of the patient's values, beliefs, readiness to change, and goals. For example, a clinician could ask:
  - *"Do you have any concerns about your use of opioid pain medications?"* or
  - *"Can you tell me a little more about how using fentanyl has affecting your relationships?"*

- Using **affirmative** words and responses can help clinicians express empathy, genuine concern, and appreciation for the patient's strengths and positive traits. Some examples of affirmative statements include:
  - *"It took a lot of courage to tell me about your use of opioids today,"* or
  - *"Sounds like you have been coping with a lot in your life recently,"* or
  - *"I appreciate you hanging in there with me as we talk about this—that takes a lot of strength."*
- **Reflective listening techniques** give clinicians a chance to verify that they are hearing a patient accurately, it builds trust and empathy, and allows the patient to correct or clarify any misunderstandings or misperceptions. An example would be:
  - *"I hear you saying that you enjoy the initial feelings of using the pain medication because it relaxes you and feels good, but that you are also concerned that you can't control your use the way you used to…is that right?"*
- **Summarization** distills the key points made in a conversation and can help point out, in a neutral way, discrepancies between the patient's current situation and what their goals or values are. Summarizing can be used multiple times in a conversation, as needed. For example:
  - *"Let me check that I understand what we've been talking about thus far: you've been worried that your use of heroin is interfering with your relationship with your husband and is costing a lot of money. You've tried to cut back or quit, but that's been difficult and you're feeling discouraged. You are open to trying some treatments but you're not sure they'll work. How am I doing?"*

Effectively using MI techniques requires that clinicians resist the common urge to advise patients about what they should do to improve their health or change their behaviors. Instead, **the goal is to elicit the patient's own motivations and reasons for change** and use those to suggest possible avenues for treatment, counseling, or other ways to support reduced substance use or abstinence. Examples of questions that respect the patient's autonomy and agency are:

- *"So where do we go from here?"* or
- *"After reviewing all of this, what's the next step for you?"* or
- *"You're the expert on you, but I can tell you what the evidence shows us about what can work and what other people have done in your situation."*

Figure 4: Summary of SBIRT process



- Conducting a brief intervention is billable. More information about reimbursement and billing can be found at SAMHSA.gov/sbirt/coding-reimbursement.
- For clinicians who are not able to provide medications for OUD, refer to an OUD treatment clinician and continue to follow-up with the patient regarding treatment.

BOTTOM LINE: Universally screen for substance use disorder using SBIRT, an evidence-based tool for identifying problematic substance use. If the results are positive, investigate further using, for example, the 5 A's approach and motivational interviewing techniques.

Medications to treat OUD

The U.S. Food and Drug Administration (FDA) has approved three medications for treating OUD: buprenorphine, methadone, and extended-release (ER) intramuscular naltrexone. All three medications can reduce cravings for and misuse of opioids.[13] However, ER naltrexone is considered a "second-line" medication due to difficulty with induction (the patient needs to go 7-10 days without opioids prior to receiving ER naltrexone) and inferior overdose reduction effects compared to methadone and buprenorphine.[28,29] Each medication has an unique mechanism of action and involves different formulations, methods of initiation and maintenance, patterns of administration, and regulatory requirements.

Table 1: FDA-approved medications for treating OUD[13]

Medication	Dosage form	Product name
Buprenorphine	Sublingual tablet	Subutex, generics
	Subcutaneous injection (extended release)	Brixadi (weekly and monthly) Sublocade (monthly)
Buprenorphine/naloxone	Buccal film	Suboxone
	Sublingual film	Suboxone, generics
	Sublingual tablet	Suboxone, Zubsolv, generics
Methadone	Liquid concentrate	MethaDose, generics
	Tablets	Dolophine, MethaDose, generics
Naltrexone	Intra-muscular injection (extended-release)	Vivitrol
	Oral naltrexone*	Revia, generics
* Oral naltrexone is not recommended or FDA-approved for long-term treatment of OUD due to high non-adherence rates; however, oral doses can be used to help patients transition to extended-release naltrexone.		

Methadone

Methadone is a synthetic, long-acting, full agonist at mu-opioid receptors.[30] This activity reduces the unpleasant/dysphoric symptoms of opioid withdrawal (please see page 25 for a further discussion of signs and symptoms of withdrawal), and, at therapeutic doses, it blunts the "highs" of shorter-acting opioids such as heroin, codeine, and oxycodone. Patients do not have to experience opioid withdrawal before starting methadone. Because methadone is long-acting, it may take days to weeks to achieve a therapeutic dose, which requires individualized monitoring to minimize cravings and reduce the risk of return to use of other opioids.

In the U.S., outpatient methadone treatment for OUD can only be given to persons enrolled in a federally-registered opioid treatment program (OTP). Note, however, that methadone can be provided when patients are admitted to a hospital for treatment of other conditions or in emergencies.[31] New patients are required to visit an OTP frequently to receive their dose. Eventually, stable patients may receive more and more take-home doses if they meet certain criteria, such as having a stable period of good functioning without illicit drug use.[24] In addition, patients on methadone are generally required to attend regular counseling sessions with clinic providers. (Note that regulations relative to methadone continue to evolve, so stay abreast of developments related to methadone-related requirements – and there may be state-based regulatory variations on top of federal regulations.)

As a full agonist opioid, methadone sustains opioid tolerance and physiological dependence, and missing doses may precipitate opioid withdrawal. A patient taking methadone to manage OUD is still at risk for overdose,[32] but that risk is significantly lower compared to people who are not in treatment.[33,34]

Common side effects of methadone are constipation, nausea/vomiting, sweating, dizziness, and sedation.

Methadone can induce respiratory depression, particularly when combined with benzodiazepines, alcohol, or other central nervous system (CNS) depressants. However, the FDA advises that methadone not be withheld from patients taking CNS depressants because the risk of overdose is even higher among patients with OUD not on methadone.[35] The other potential harms of methadone include hypogonadism, which is a common side effect of chronic use of any opioid, and QTc segment prolongation. Opioid treatment programs may require monitoring of patients' QTc, especially for older patients, those on higher doses, after dose increases, or on other medications that also affect the QTc interval. Because methadone is metabolized by CYP3A4 liver enzymes (also involved in the metabolism of many common medications such as anticonvulsants, antibiotics, antidepressants, and antiretrovirals), clinicians may need to adjust other prescribed medications affected by the patient's required methadone dose, and it is recommended that drug interaction safety searches be used when prescribing to patients receiving methadone maintenance.[30]

Buprenorphine

Buprenorphine is a high-affinity, partial agonist at mu-opioid receptors as well as an antagonist at the kappa and delta opioid receptors.[36] Like methadone, buprenorphine can relieve opioid withdrawal symptoms, and, because of its high competitive affinity for the opioid receptors, it can reduce the rewarding effect of other opioids. Buprenorphine's partial agonist mechanism is associated with a significantly lower risk for respiratory depression compared to methadone and other full-agonist opioids,[37] and a therapeutic dose may be achieved within a few days.[38] The risk of opioid overdose declines immediately when patients with OUD initiate buprenorphine treatment.[34]

Buprenorphine undergoes extensive first-pass metabolism in the liver and has very low oral bioavailability.[39] Its bioavailability via non-oral routes of administration, however, is extensive enough to make it viable for the treatment of OUD. Buprenorphine (for the indication of OUD) is available as sublingual tablets, sublingual/buccal films, and as an extended-release subcutaneous injection (Table 1). Some film and tablet formulations are combined with the opioid antagonist naloxone to discourage misuse by dissolving and injecting the medication–these combination formulations are generally considered standard-of-care and are the forms used most often for OUD treatment. Some formulations of buprenorphine are only FDA-approved to treat pain and not OUD, including a buprenorphine-only patch (Butrans) and a buprenorphine-only buccal film (Belbuca).

All formulations of buprenorphine decrease opioid misuse, reduce risk of overdose, and increase negative urine drug screens compared to no treatment.[40] The monthly subcutaneous injection Sublocade require that patients be stabilized on transmucosal buprenorphine for a week prior to initiation while the weekly subcutaneous injection Brixadi may be initiated after a single 4 mg buprenorphine dose to ensure the patient will not have precipitated withdrawal.[41]

Buprenorphine can be prescribed in a primary care setting. As of January 2023, in order to prescribe buprenorphine, eligible clinicians in the U.S. must have a Drug Enforcement Administration (DEA) license with authority to prescribe Schedule III medications.[42] Prior requirements for a DEA waiver to prescribe buprenorphine for the treatment of OUD and limitations on the number of patients treated have been removed.[42] Despite this federal removal of limitations, state requirements may be more stringent. Know what, if any, state requirements apply for the prescribing of buprenorphine.

Similar to methadone, buprenorphine sustains opioid tolerance and physiological dependence in patients, so discontinuation can result in withdrawal—although buprenorphine's withdrawal symptoms may be less

severe compared to those associated with methadone. The most common side effects are constipation, vomiting, headache, sweating, insomnia, and blurred vision. The risk of hypogonadism and QTc prolongation is lower with buprenorphine compared to methadone.[43]

Buprenorphine (as well as naltrexone) can increase the risk of precipitating acute opioid withdrawal if the patient has recently used any other opioid. This is because of buprenorphine's high binding affinity for the opioid receptor, which allows it to displace other opioids from these receptors.[13] Thus, in a standard buprenorphine initiation, a patient must be in mild to moderate opioid withdrawal prior to initiation to avoid exacerbating the withdrawal. Alternative buprenorphine initiation strategies (informally referred to as "microdosing," "microinduction," or "macrodosing") are discussed in detail below.[44] Alternative induction strategies may help minimize withdrawal symptoms, reduce dropout rates during initiation, and reduce patient fears of withdrawal.[45]

Buprenorphine has very few clinically significant drug interactions, with common exceptions being delavirdine, atazanavir, and rifampin.[46] Comparative efficacy data on different buprenorphine formulations are limited.

Extended-release naltrexone

Naltrexone is not an opioid. It is a full antagonist at the mu-opioid receptor, which blocks both the euphoric and analgesic effects of all opioids, including endogenous opioids (e.g., endorphins), and also reduces cravings for opioids, through reduced anticipated reward and extinction learning.[36] Naltrexone does not cause physiological opioid dependence, nor does it produce any of the rewarding effects of opioids. Patients may try to use opioids while on ER naltrexone, but it is unlikely that they will experience rewarding effects from such use, unless naltrexone's effect is overcome by other drugs.[13]

Intramuscular gluteal injection of ER naltrexone is administered in the clinician's office, and no additional training is required for administration. The most common side effects of ER naltrexone are injection site pain, nasopharyngitis, nausea, insomnia, and toothache.

Medical detoxification is required prior to administering naltrexone, with a typical waiting period of 7-10 days, although up to 14 days if the drug being used is fentanyl. Various medications can be used during the detoxification period to help ease withdrawal symptoms, including short-term use of methadone or buprenorphine, or non-opioid agents such as clonidine or lofexidine. The waiting period prior to naltrexone initiation can pose a significant barrier because of the high risk for opioid relapse and/or drop out from care as the patient endures opioid withdrawal symptoms.[13] Strategies to support the transition to ER naltrexone include referral to residential level of care following detoxification, or enlisting community recovery supports (loved ones, recovery peers) and referral to more intensive outpatient treatment programming.

Naltrexone is currently available both as a once-daily oral tablet and a once-monthly, ER intramuscular depot injection (Vivitrol). The oral formulation is not used for OUD, because it was found to be no better than placebo in a 2011 Cochrane review of 13 trials with 1,158 participants due to very high rates of medication non-adherence.[47]

One major risk of naltrexone is the loss of opioid tolerance leading to high risk of overdose if patients return to opioid use after naltrexone is discontinued. Large, randomized controlled trials of ER naltrexone for OUD do not support earlier reports that naltrexone is associated with depression or dysphoria in this population; in fact, stabilization with naltrexone is associated with mood improvement in patients with OUD.[48-51]

Naloxone vs. Naltrexone: What's the difference?

Naloxone (Narcan) or nalmefene (Opvee) are opioid antagonists given by injection or nasal spray to reverse overdoses. Both act within minutes. Naloxone lasts for only about an hour due to rapid metabolism, while nalmefene lasts for one to four hours.

Naltrexone has a very similar chemical structure to naloxone and is also an opioid antagonist, but it acts more slowly and lasts longer. Extended-release naltrexone (Vivitrol) is a gluteal intramuscular injection used clinically to reduce substance use and cravings for opioids and alcohol.

BOTTOM LINE: The three FDA-approved medications approved for OUD are methadone, buprenorphine, and ER naltrexone. All three are safe, but each has a distinct mechanism of action, method of administration, and possible side effects.

Evidence supporting use of medications for OUD

Abundant evidence from decades of randomized trials, clinical studies, and meta-analyses demonstrates that agonist or partial-agonist opioid treatments provide the easiest transition for active users to stop non-prescribed opioid use, and are supported by the greatest safety data across all OUD populations.[13,38] The evidence base for ER naltrexone is less robust than for methadone or buprenorphine.[13] The outcomes used to demonstrate efficacy vary between studies and include decreases in: illicit opioid use (often measured by urine toxicology testing), drug-related overdose deaths, self-reported use and cravings, and all-cause mortality, and increases in treatment retention rates.

As demonstrated by the data below, people with OUD treated with methadone or buprenorphine are less likely to die, less likely to overdose, and more likely to remain in treatment. Using medication to treat OUD is also associated with improved social functioning and quality of life compared to people not on medications.[24]

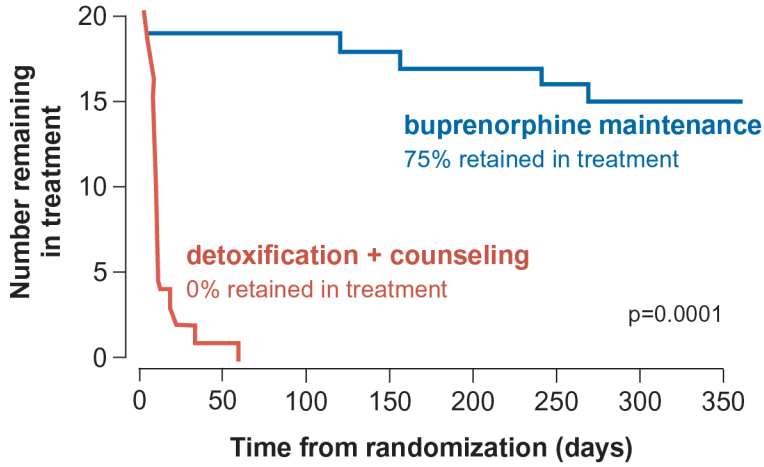
Buprenorphine

A 2014 Cochrane review of 31 trials with 5,430 OUD patients evaluated buprenorphine maintenance therapy (sublingual solutions, sublingual tablets, or implants) compared to either placebo or methadone. Buprenorphine was superior for retaining patients in treatment compared to placebo at low doses (2-6 mg) (relative risk [RR] 1.5; 95% CI: 1.19-1.88), medium doses (7-15 mg) (RR 1.74; 95% CI: 1.06-2.87), and high doses (≥ 16 mg) (RR 1.82; 95% CI: 1.15-2.9).[52] Low or flexible doses of buprenorphine were less effective than methadone for patient retention, but at medium or high doses of buprenorphine, no significant differences in treatment retention were observed. Currently, with the significantly increased rates of fentanyl abuse, it is rare that anyone is given less than 16mg/day of buprenorphine, hence what

was considered “high dose” at the time of the Cochrane review is actually “low to usual dose” in the current era. Recent data also show that patients prescribed a 24 mg/day dose of buprenorphine remained in treatment longer than those prescribed 16 mg/day (adjusted hazard ratio 1.20, 95% CI 1.06-1.37).[53]

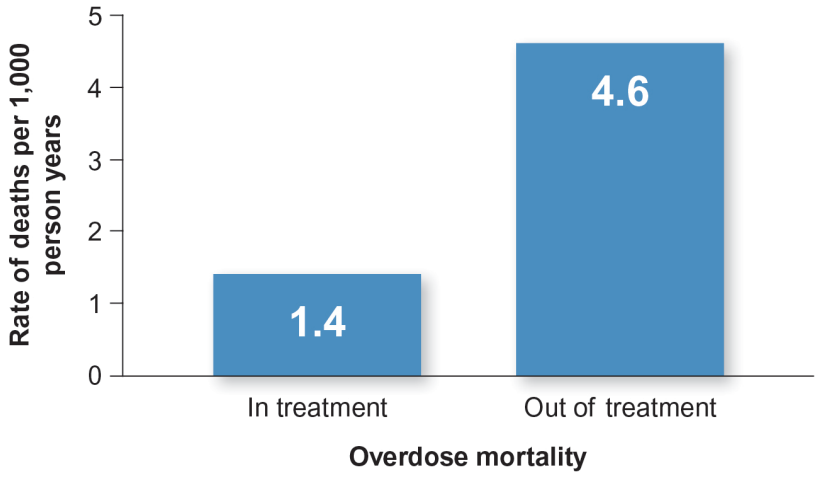
A small trial in Sweden randomized 40 adults with OUD to daily buprenorphine 16 mg sublingually for one year vs. a six-day taper of buprenorphine followed by placebo.[54] After one year, 75% of patients on buprenorphine remained in treatment and were abstinent vs. 0% in the placebo group, and 20% of those in the placebo group died. No deaths occurred in the buprenorphine group.

Figure 5: Buprenorphine associated with improved treatment retention[54]



A prospective cohort study following 15,831 patients with OUD treated with buprenorphine for up to 4.5 years showed that the rate of overdose mortality was four times higher in patients who stopped taking buprenorphine (4.6 deaths per 1000 person years; 95% CI: 3.9-5.4 deaths per 1000 person years) compared to patients who remained on the medication (1.4 deaths per 1000 person years; 95% CI: 1-2 deaths per 1000 person years).[34]

Figure 6: Increased mortality associated with cessation of buprenorphine[34]

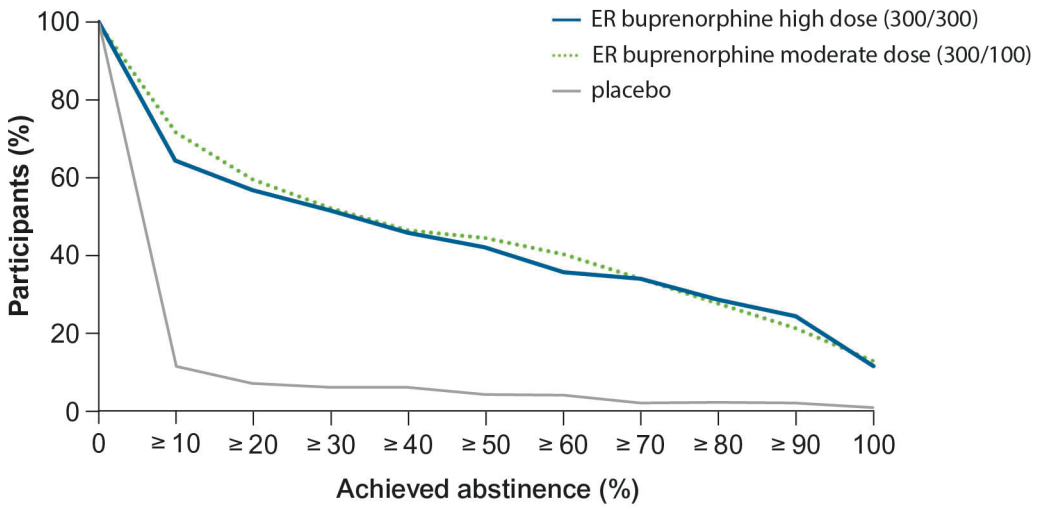


The efficacy of buprenorphine was also demonstrated in a 2015 trial that randomized 329 emergency department patients with OUD to one of three interventions: standard referral for treatment; brief

intervention that included facilitated referral to community-based treatment; or brief intervention and buprenorphine initiation.[55] At 30-day follow-up, 78% of the buprenorphine group remained in treatment vs. 37% in the referral group and 45% in the brief intervention group (p<0.001 for both comparisons). No significant between-group differences were observed for self-reported illicit opioid use in the prior week or in rates of urine samples testing negative for opioids.

Extended-release (ER) formulations of buprenorphine, which have the advantage of both facilitating care for patients unable to take a medication daily and minimizing risk of diversion, are also efficacious and safe. One randomized controlled trial in 2019 recruited 504 patients with moderate to severe OUD who had not recently been on medications for OUD and randomized them to ER buprenorphine high dose (300 mg for six monthly doses), ER buprenorphine moderate dose (300 mg for two monthly doses followed by 100 mg for four monthly doses) or placebo injections. The patients receiving ER buprenorphine had significantly higher rates of abstinence (41% and 43%, respectively) compared to placebo (5%).[56]

Figure 7: Extended-release buprenorphine is also effective at preventing return to opioid use[56]

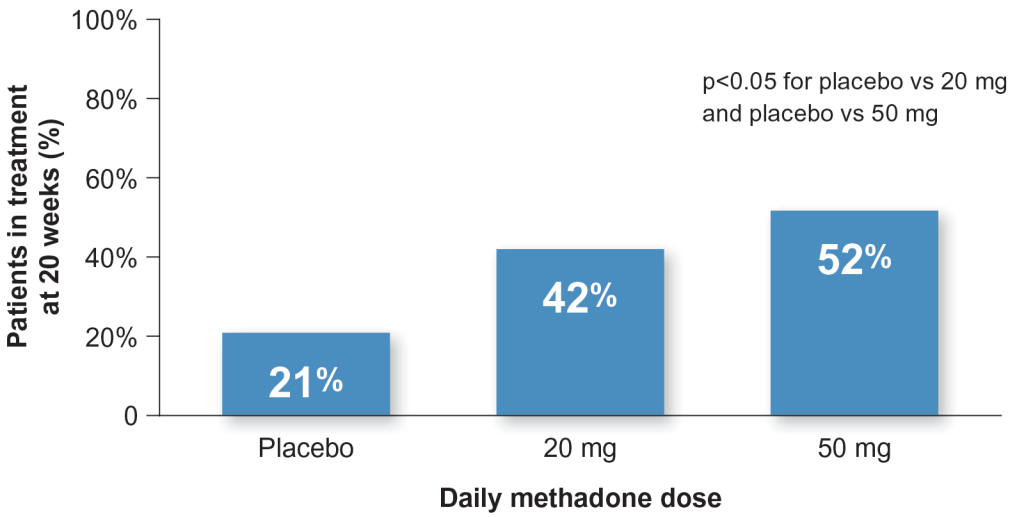


The efficacy of depot buprenorphine (i.e., weekly or monthly subcutaneous injections of the Brixadi formulation of buprenorphine) compared to daily sublingual buprenorphine was evaluated in a non-inferiority randomized trial (N=428).[57] Response rates (defined as no evidence of illicit opioid use at prespecified time points) were higher in the depot group compared to the sublingual group (17.4% vs. 14.4%, P<0.001). The proportion of opioid-negative urine samples was also higher in the depot group: 35.1% vs. 28.4%, P< 0.001).

Methadone

Across all populations, methadone is associated with higher retention rates compared to placebo. One trial randomized 247 patients to three groups: counseling alone, counseling plus methadone 20 mg/day, or counseling plus methadone 50 mg/day.[58] Both methadone doses were more effective than counseling alone at 20 weeks (P<0.05 for both comparisons).

Figure 8: Methadone significantly improved treatment retention at 20 weeks[58]

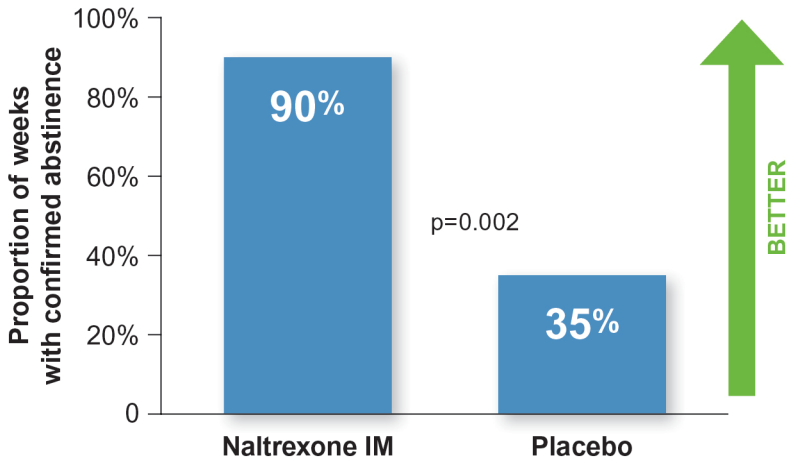


A trial comparing methadone maintenance therapy plus psychosocial therapy vs. a detoxification regimen that included psychosocial therapy, education sessions, and group therapy found significantly higher lengths of treatment retention with methadone maintenance therapy (median 438.5 days vs. 174 days, P<0.001).[59] Heroin use in both groups dropped markedly from baseline, with the decrease greater in the maintenance group during the last 6 months of treatment.

Naltrexone

Although the evidence base for intramuscular (IM) ER naltrexone is less robust than for methadone or buprenorphine, naltrexone has been shown to significantly decrease opioid misuse in patients with mild-to-moderate OUD.[13,60] For example, one trial randomized 250 patients with OUD who completed inpatient detoxification (≥7 days off all opioids) to 24 weeks of naltrexone intramuscular injection (380 mg/month) vs. placebo.[61] At 24-week follow-up, 90% in the naltrexone group were abstinent compared to 35% in the placebo group (P=0.002).

Figure 9: Improved abstinence with naltrexone vs. placebo[61]



The 2018 open-label X:BOT trial randomized 570 adults with OUD to monthly ER naltrexone vs. daily self-administered buprenorphine/naloxone sublingual film.[60] Overall relapse rates were higher with ER naltrexone (65% vs. 57%; HR 1.36; 95% CI: 1.1-1.68) with most of the difference accounted for by the 89% rate of initiation failure in the ER naltrexone group. Among those successfully initiated, there was no significant difference in relapse rates between groups.

Because of the challenges in initiating ER naltrexone and its reduced efficacy in preventing overdose, methadone and buprenorphine are the preferred options for treating OUD.

Comparative effectiveness of OUD medications: buprenorphine vs. methadone

A 2016 Cochrane review of six trials (n=607) of patients with prescription opioid misuse found no significant differences between methadone and buprenorphine on a range of outcomes. The mean study duration was 24 weeks, and no significant differences were found for days of unsanctioned opioid use (standardized mean difference -0.31; 95% CI: -0.66 to 0.04), self-reported opioid use (RR 0.37; 95% CI: 0.08-1.63), or positive urine screens for opioid use (RR 0.81; 95% CI: 0.56-1.18).[62]

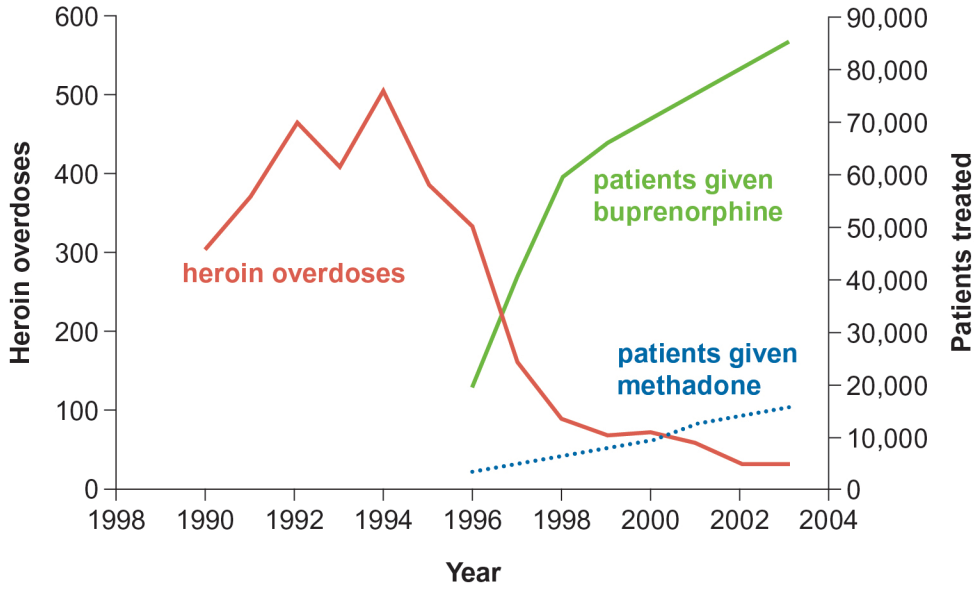
A 2014 Cochrane review of 31 trials involving 5,430 opioid-dependent persons (including dependence on both prescription and illicit opioids) found that buprenorphine administered in flexible doses adjusted to patient needs was slightly less effective than methadone for retaining participants in treatment (RR 0.83; 95% CI: 0.72-0.95).[52] For those retained in treatment, no difference was observed in suppression of opioid use (measured by urinalysis or self-reported use).

A follow-up study (mean follow-up 4.5 years) evaluated a trial that initially randomized 1,080 patients with OUD to treatment with buprenorphine vs. methadone for at least 24 weeks (with option for long-term maintenance treatment).[63] Mortality at follow-up was 3% in the buprenorphine group vs. 6% in the methadone group (not significant), and illicit opioid use was higher in the buprenorphine group (43% vs. 32%, P<0.01).

Population-level data

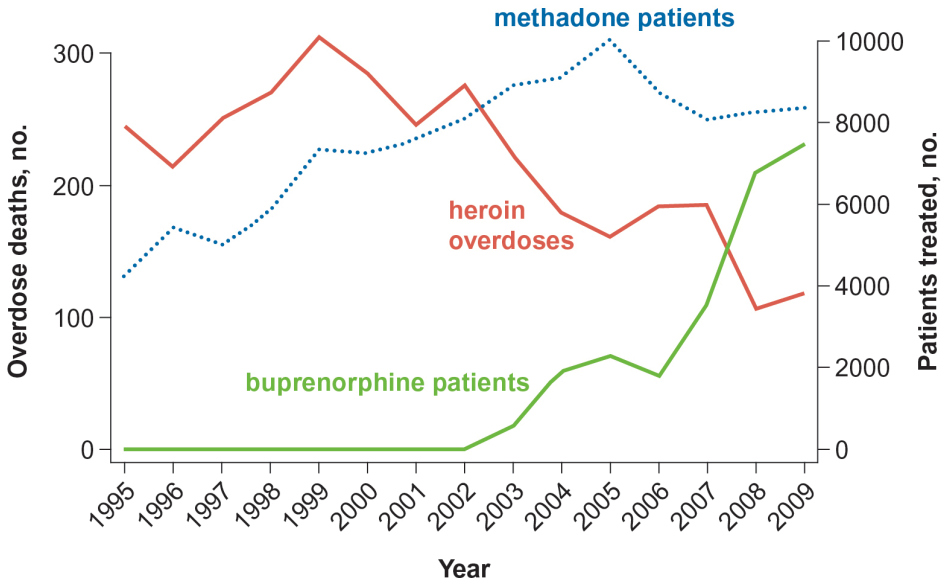
Compelling evidence for the efficacy of medication-based treatment also comes from population-level studies. Facing rising levels of heroin overdoses in the 1990s, France, in 1996, increased the availability of methadone and buprenorphine by allowing primary care clinicians to prescribe both medications without getting additional certifications (both medications were also subsidized by the government).[64] As illustrated in Figure 10, heroin deaths declined rapidly as use of medication treatment increased.

Figure 10: Impact on heroin overdoses with rising use of methadone and buprenorphine[64]



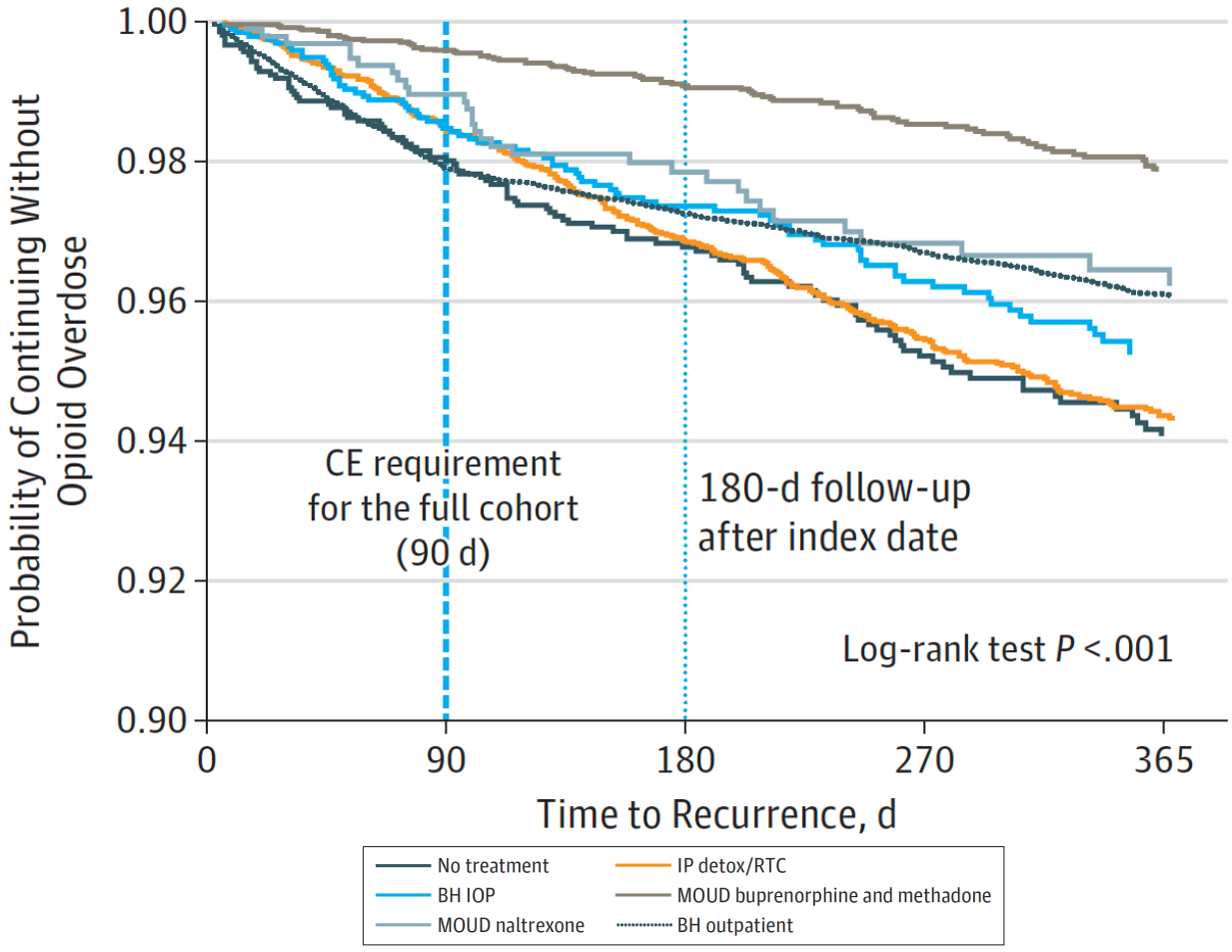
A similar pattern was observed in Baltimore, where overdose deaths declined as use of buprenorphine increased (Figure 11).[65]

Figure 11: Comparison of relapse rates in Baltimore with different OUD treatments[65]



A 2020 retrospective study compared opioid-related overdose or emergency department use or hospitalization associated with a primary opioid diagnosis at 3 and 12 months after treatment with one of the following: no treatment, inpatient detoxification, intensive behavioral health, buprenorphine or methadone, naltrexone, non-intensive behavioral health. Only buprenorphine or methadone treatment was associated with reduced risk for overdose and acute care use compared to the other treatments.[28]

Figure 12: Only patients who receive buprenorphine or methadone for OUD are less likely to experience an opioid overdose[28]



BH = behavioral health; BH IOP = intensive behavioral health (intensive outpatient or partial hospitalization); MOUD = medication for OUD; IP detox/RTC = inpatient detoxification or residential services; CE = continuous enrollment

BOTTOM LINE: Buprenorphine, methadone, and ER naltrexone can all reduce the risk of overdose death, improve treatment retention, reduce cravings, and decrease opioid misuse, although buprenorphine and methadone treatments are easier to initiate and have superior patient retention rates and reduced risk of overdose compared to ER naltrexone.

OUD management

As with any chronic condition, the goal of treatment for OUD is to prevent and manage acute and chronic complications, and to improve functionality and wellbeing. Importantly, recurrence of opioid use can occur while on treatment and does not imply "treatment failure." Following a diagnosis of OUD, a management plan should be created that includes the following components:[24]

- assessment for, and treatment of, medical and psychological comorbidities
- use of motivational interviewing techniques to promote safer behaviors and to encourage patient engagement with treatment
- opioid overdose education and naloxone distribution
- education and safety planning for those with a history of suicidal ideation or attempt[66]
- education about harm reduction and safer injection drug techniques (if patient is known to be using injectable drugs) and sources of sterile needles (which can be prescribed)
- timely in-person or virtual follow-up, regardless of whether the patient was referred for specialty treatment

Prescribe naloxone

Naloxone (e.g., Narcan, Evizio, available in over-the-counter formulations) and nalmefene (Opvee, FDA approved in May, 2023) are both opioid receptor antagonists that can quickly reverse symptoms of opioid overdose and save lives.[67]

In 2020, the FDA recommended that all health care professionals prescribing opioid pain medications and medications to treat OUD discuss naloxone with patients.[68]

Additionally, naloxone is recommended for anyone who:

- is in treatment for OUD
- has a history of opioid overdose risk factors (e.g., prior non-fatal overdose, using alone)
- is using ≥50 MME/day
- is using any opioid and has COPD, sleep apnea, other respiratory conditions, renal or hepatic dysfunction, or a mental health condition
- has a prescription for both an opioid and a benzodiazepine
- has lost opioid tolerance due to abstinence (e.g., recently released from prison, withdrawal management or residential treatment programs)
- is a family member/significant other of person in treatment for substance use disorder or at risk for opioid overdose

A 2019 study found a significant association between the adoption of state laws providing direct authority to pharmacists to prescribe naloxone and lower rates of fatal overdoses.[69] In states with such policies, opioid-related fatal overdoses dropped by 0.387 per 100,000 people ≥3 years after adoption of the laws (95% CI: 0.119-0.656).

Many states have adopted standing pharmacy orders to allow patients (or their caregivers and family members) to obtain naloxone without a prescription. However, we recommend that individual clinicians prescribe naloxone when possible because it offers an opportunity for discussing overdose risk associated with OUD or with prescription opioids, and because it may expedite insurance coverage for some patients.

Biopsychosocial assessment

The American Society for Addiction Medicine (ASAM) has created standards for conducting comprehensive biopsychosocial assessments to help guide decisions about patient care and treatment.[70] The ASAM criteria allow clinicians to rate a patient's risk along 6 dimensions:

- Acute intoxication and/or withdrawal potential
- Biomedical conditions and complications
- Emotional, behavioral, and cognitive conditions and complications
- Readiness to change
- Relapse, continued use, or continued problem potential
- Recovery/living environment

Answers to the questions associated with each dimension will drive decisions about what kinds of supports a patient needs, how intense the treatment and/or monitoring will need to be, and/or what kinds of mental/emotional therapies might be most appropriate. However, the most important feature in determining a treatment plan is the patient's interest and engagement – which is not necessarily well-captured in the ASAM criteria.

Practical advice for selecting a medication for OUD

As described in the section summarizing efficacy, buprenorphine, methadone and ER naltrexone all have evidence of efficacy in the treatment of OUD.[24] For most patients, buprenorphine or methadone are the first-line options, and ER naltrexone is second line given its less robust effectiveness and need to abstain from opioids prior to initiation. Medication choice for treatment of OUD is guided by OUD severity, the patient's need for additional psychosocial support and/or monitoring, patient preference, logistical issues, and patient willingness to undergo full opioid withdrawal (in the case of ER naltrexone). The choice of treatment should always be a shared decision between the health care professional and patient, with attention to the fact that treatment setting can be more important than attributes of the medication itself. In the primary care setting, buprenorphine is the preferred treatment option for OUD.

The major relevant factors for treatment selection are summarized in Table 2. Although medication to treat OUD is often provided along with behavioral or cognitive-behavioral therapy, medications are effective with or without psychosocial treatment.[71] As a result, medication therapy for OUD should not be withheld due to a lack of access to concurrent behavioral therapy.

Table 2: Medication choices for treating OUD

Category	Buprenorphine*	Methadone	Naltrexone injection
Mechanism of action	 **Partial agonist:** partially activates opioid receptor	 **Full agonist:** activates opioid receptor	 **Antagonist:** blocks opioid receptor
Who can provide treatment	any prescriber with a DEA license**	federally-regulated opioid treatment program or inpatient/emergency department	any prescriber
Dosage forms	sublingual film or tablet, buccal film, or long-acting injection	liquid or tablet	long-acting intramuscular injection†
Treatment delivery	no daily clinic visits required	supervised daily administration or limited take-home treatment	monthly injection
Patient characteristics	patients who prefer an opioid agonist without frequent clinic visits	patients with multiple unsuccessful prior treatment attempts, and/or who need daily structured support	• patients who can be abstinent from opioids for 7-10 days prior to starting • patients who cannot use agonist therapy

Keep abreast of changing regulations regarding access to MOUD.

*Buprenorphine is often combined with naloxone in a sublingual formulation (e.g., Suboxone) to prevent misuse if injected; naloxone in sublingual formulations has little or no effect if taken as prescribed. **The DEA license needs to have Schedule III authority. †While not recommended, oral naltrexone may be use for patients unwilling or able to use other options.

Psychosocial treatments

Psychosocial treatment is generally recommended in conjunction with medication to treat OUD, although the lack of psychosocial support should not be an impediment to the use of medications.[13,40] Although the best outcomes are typically achieved with a combination of medication and behavioral therapies, evidence suggests that medication-based treatment alone is as effective as the same regimen plus formal psychosocial therapy.[13] For example, a 2012 trial randomized 230 adults with OUD to one of three groups: methadone without extra counseling; methadone with standard counseling; or methadone with counseling in the context of smaller caseloads.[72] At one-year follow-up there were no significant differences between the groups in rates of retention in treatment or positive urine tests for opioids. Three other randomized trials comparing buprenorphine with standard management (which included some

counseling) vs. buprenorphine plus cognitive behavioral therapy or extra counseling sessions also found no significant differences in key opioid-related outcomes.[73-75]

Nonetheless, psychosocial, behavioral, and peer-support interventions may provide many important benefits for patients beyond strictly opioid-related outcomes, such as reducing suicide risk, improving self-confidence, self-advocacy, general quality of life, and improvements in legal, interpersonal, and occupational functioning.[13,76]

Psychosocial treatment, which helps treat the "whole patient" can include:[77]

- psychosocial needs assessment
- supportive counseling (e.g., motivational interviewing)
- links to existing family supports
- referrals to community services
- linkage with mutual-help peer support groups such as Narcotics Anonymous (NA), Alcoholics Anonymous (AA), and SMART Recovery

Among evidence-based psychosocial treatments, the most effective option for OUD is contingency management (CM), which provides immediate positive reinforcers for treatment engagement and progress; unfortunately, CM is not available in most U.S. patient care settings.[78]

Peer support workers (sometimes also called peer navigators, peer advocates, or lived experience workers) have been shown to facilitate treatment for substance use disorders and to contribute to treatment retention and recovery.[79] Peer support groups such as NA, AA, and SMART Recovery provide communities in which new, safe social relationships can be formed. These programs have not been rigorously evaluated with randomized trials, though long-term experience with these networks suggests that some patients find the structure helpful to achieve and maintain recovery. The acceptance of medications for OUD among peer support groups continues to shift; some are accepting while others are less so. This varies significantly by region and by individual meetings (i.e., one AA or NA group may have different cultural acceptance from another). Additionally, online virtual peer supports are broadly offered all day at intherooms.com.

Toxicology testing

In the context of OUD, toxicology testing is intended to be used as a tool to support recovery and improve medication safety; it should *not* be used as a coercive tool to dismiss patients from practice or to reduce access to MOUD.[80] When the right test is selected for the right person at the right time, toxicology testing can help clinicians:[80]

- explore denial, motivation, and actual substance use behaviors that patients exhibit
- monitor patients for adherence and/or diversion
- make therapeutic decisions when toxicology testing results contradict a patients self-reported use
- reinforce abstinence from non-prescribed substances

Toxicology testing results are intended to answer a very narrow question for clinicians: whether a certain substance was detected in the patient's sample. The evidence to support toxicology testing in the management of OUD is currently based primarily on expert consensus as articulated in various guidelines.[40,80,81]

Toxicology testing is recommended as part of the patient's initial assessment, when starting medication treatment, weekly during the initial phase, and monthly when the patient is stable. Experts recommend that the tests be conducted at random. There are many factors that the clinician should consider:[80]

- stability of the patient
- type of treatment
- treatment setting
- half-life of drugs in the matrix (e.g., urine, saliva, hair) being tested

Although urine toxicology testing has the most evidence supporting it, sometimes urine toxicology testing is not possible and other matrices (e.g., saliva, hair) can be used, although clinicians need to be aware that different matrices have varying windows of detection. Clinicians also need to be able to interpret testing results and have a plan to address those results (for assistance with interpreting unusual results please ask your local medical toxicologist). Studies show that even clinicians who are experts in addiction and pain were only able to correctly interpret three out of seven urine toxicology screen results.[82] Prior to ordering toxicology testing, clinicians should ask the patient when the last dose of a prescribed opioid (including buprenorphine) was taken.

A positive toxicology test indicates the patient had a detectable amount of the targeted substance when the sample was collected. Sometimes confirmatory testing may be required (i.e., liquid chromatography-mass spectrometry) due to high false positivity rates of the urine toxicology screen.[83] A positive toxicology test does *not*:[80]

- provide enough evidence for a substance use disorder diagnosis
- explain whether a patient's symptoms are caused by the presence of the substance
- measure patient's degree of clinical or functional impairment
- measure a patient's pattern of use over time (may require more than one confirmed, aberrant test result)

Repeated positive test results may signal a range of scenarios, including that a patient:[80]

- is not taking some or all of their medication or may be taking the medication incorrectly
- may need a different medication
- may need directly observed medication administration in the office or at an outpatient treatment program (OTP)
- may need a buprenorphine dose increase
- may need more counseling or a higher level of a specialty addiction treatment program
- may need to participate in recovery support services[24]

It is important not to over-interpret a negative toxicology test result: it simply means the patient either has not used the substance in the targeted window of detection or used so little is it not detectable. A negative toxicology test does not mean the patient has not used nor can this result be used to rule out any substance use disorder.

There is limited evidence supporting the frequency of urine toxicology screening in health outcomes of people with OUD. Evidence suggests that urine toxicology screening frequency reflects philosophy rather than clinical needs or outcomes.[84] Therefore, be cautious when interpreting and using urine toxicology testing for patients with OUD. As evidence of their limited utility, during the Covid-19 pandemic, the transition to telemedicine and disruption of routine frequency toxicology testing for patients with OUD has

not translated to poorer patient outcomes.[85,86] Use of toxicology testing in OUD treatment should be customized for the clinical setting and personalized to individual patient factors.

Treatment duration

OUD guidelines do not recommend a duration of treatment with medication. Treatment could continue for an indefinite period because of the high risk of return to use and overdose with discontinuation and because of the chronicity of the disease.[13] For example, a population-based retrospective study of 14,602 patients who discontinued methadone treatment found that only 13% had successful outcomes (no treatment re-entry, death, or opioid-related hospitalization) within 18 months.[87]

Nonetheless, some patients who have stable OUD managed with opioid agonist therapy may wish to stop medication treatment. An ideal time frame for a trial of medication tapering has not been established. Tapering should always be at the patient's discretion, and all decisions should be based on a thorough dialogue between patient and clinician. Studies show that there is no difference between a short (7 day) vs a long (28 day) taper of buprenorphine as measured by opioid-free urine drug screens. In real practice, much slower and longer taper routines are better tolerated with ongoing treatment retention. The success of the taper should be framed in the context of functional goals that are important to the patient, such as maintaining employment, avoiding relapse, or continuing with social/emotional support programs.[88] It is very important that a patient remain under medical or behavioral monitoring following a completed taper, due to high rates of return to opioid use in the 6-12 months following discontinuation.

BOTTOM LINE: Primary care clinicians can support patients with OUD by screening, diagnosing, initiating treatment, and by regularly monitoring patient progress. Medication choice and treatment setting selection are equally important, and the decision to start treatment should be shared between the patient and clinician. Opioid antagonist overdose reversal agents (e.g. Naloxone/Narcan) can save lives and should be prescribed to patients with OUD and others at high risk for experiencing or responding to an opioid overdose.

Buprenorphine prescribing

As the evidence presented above clearly shows, buprenorphine is one of the most effective and life-saving interventions primary care clinicians can offer their patients, and fortunately it is safe and relatively simple to prescribe. The most common formulation used in primary care settings is buprenorphine-naloxone sublingual films (Suboxone, generics).

Table 3. Factors for buprenorphine initiation based on high-tolerance and high-potency synthetic opioid exposure[89]

Situation	Outpatient	Emergency department	Residential or hospital setting
Opioid withdrawal COWS ≥ 8 with 1 objective sign of opioid withdrawal	Standard dose OR high dose	Standard dose OR high dose	Standard dose OR high dose
Opioid withdrawal COWS < 8	Standard dose OR low dose with opioid continuation	Standard dose OR low dose with opioid continuation	Standard dose OR low dose with opioid continuation
Pain + opioid withdrawal COWS < 8	Standard dose OR low dose with prescribed full agonist opioid continuation	Standard dose OR low dose with prescribed full agonist opioid continuation	Full agonist opioid with low dose buprenorphine

Buprenorphine treatment typically occurs in four phases:

1. evaluation (of OUD severity and risk of precipitated withdrawal)
2. patient education
3. initiation
4. maintenance

Evaluation

Prior to initiating buprenorphine, patients should be evaluated 1) to ensure they meet criteria for OUD (as detailed previously) and 2) to determine their risk of precipitated withdrawal. A patient's risk of precipitated withdrawal is determined based on:

- whether a patient is physically dependent on full opioid agonists
  - If a patient is NOT physically dependent (for example, intermittently using oxycodone or fentanyl every couple days) they are not at risk for precipitated withdrawal
- if they are dependent, which opioid they are primarily using before transitioning to buprenorphine.
  - Patients using extremely long-acting opioids, including fentanyl, are at high risk for precipitated withdrawal.

Patient education

Once the clinician and patient agree on starting buprenorphine and the patient's risk for precipitated withdrawal has been evaluated, the clinician should educate the patient about the following:

- Buprenorphine is an opioid, so discontinuation can lead to withdrawal and loss of opioid tolerance (that would predispose to overdose if other opioids are used). If the patient is receiving buprenorphine for the first time, it is advisable to avoid driving on the initial dosing day.
- Patients should notify clinicians of any medication changes or upcoming procedures that might require opioid pain medication

- Sublingual buprenorphine (used most commonly) should be placed under the tongue until it dissolves. Patients should not eat or drink while it is dissolving. Patients should also avoid smoking or vaping in the 30 minutes prior to dosing for optimal absorption.
- On initiation, buprenorphine can lead to precipitated withdrawal; this is usually avoided by waiting for moderate withdrawal symptoms to emerge, but other comfort medications can also be helpful (reviewed below) if this occurs.

Patients should then be given information on how to initiate buprenorphine at home and offered apps that can help guide them (see below).

Buprenorphine initiation strategies for patients with OUD

As the opioid epidemic evolves and substances of misuse change to include primarily fentanyl and other novel substances, the ways to initiate buprenorphine have shifted as well; fentanyl's long and unpredictable half-life has made precipitated withdrawal more of a problem for buprenorphine initiation. Currently three different strategies to start buprenorphine are being used: low dose, classic/standard dose, and high dose. The actual protocols that describe the initiation strategies vary from practice to practice but central components of each can help identify which patients are candidates for each dosing strategy. To date, there are no randomized trials supporting use of one protocol over another – it is a matter to be decided between clinician and patient, based on individual needs.

Precipitated withdrawal

As described previously, buprenorphine is a partial agonist with less intrinsic activity at the mu opioid receptors than full agonists. It also has very high binding affinity for the mu opioid receptor. If a patient with opioid dependence has their mu opioid receptors saturated with a full opioid agonist, buprenorphine will displace this full agonist and cause acute withdrawal symptoms (termed "precipitated withdrawal"). A common misconception is that the naloxone component in buprenorphine-naloxone causes the precipitated withdrawal; this is false, and it is the buprenorphine itself that causes precipitated withdrawal. Naloxone is minimally absorbed when taken sublingually.

Table 4: Opioid half-life determines length of time to wait before initiating buprenorphine and risk of precipitated withdrawal

Category	Examples	Time to wait before initiating buprenorphine
Short half-life	Hydromorphone, oxycodone, heroin	12-24 hours
Long half-life	Extended-release oxycodone or morphine	36 hours or more
Extremely long half-life (and related to lipophilic stores)	Methadone, fentanyl*	48 hours or more

* When used in medical settings for sedation and analgesia, fentanyl has a short half-life (3-7 hours).[90] However, when fentanyl is used illicitly for prolonged periods these kinetics change in ways that are not well understood. One study of 12 patients in residential treatment found the mean time to fentanyl clearance in urine samples was seven days from date of last use. Typically for a short-acting opioid clearance occurs in two to four days.[91]

Common signs of opioid withdrawal include:

- restlessness, irritability, anxiety
- insomnia
- yawning
- abdominal cramps, diarrhea, vomiting
- dilated pupils
- sweating
- piloerection
- elevated heart rate

Healthcare professionals can use the validated 11-item COWS to assess withdrawal severity.[92] A link to a printable version of this tool can be found at drugabuse.gov/sites/default/files/files/ClinicalOpiateWithdrawalScale.pdf

Precipitated withdrawal can be avoided by either:

- **Classic initiation**: waiting to initiate buprenorphine until a patient is in moderate withdrawal, meaning a significant amount of their mu opioid receptors are unoccupied, assessed by moderate withdrawal symptoms (e.g., Clinical Opiate Withdrawal Scale [COWS] ≥13)
- **Low dose or micro-dose initiation:** introducing small amounts of buprenorphine while a patient is still taking their full opioid agonist, escalating the buprenorphine dose until a threshold dose (typically 4mg twice daily) at which time many of their mu opioid receptors are occupied by buprenorphine.
- **Higher dose or macro-dose initiation**: dosing of 16mg at once (and up to 32 mg) sublingual buprenorphine to saturate opioid receptors within hours of initiation, which may minimize precipitated withdrawal

Classic dose buprenorphine

In a standard buprenorphine initiation, the medication is administered when a person with OUD has not used any short-acting opioids for 12 to 24 hours and experiences moderate withdrawal symptoms. For someone who has been using long-acting opioids, typically the wait is 24-48 hours after last use.

After experiencing these withdrawal symptoms, patients can be induced starting with 2 to 4 mg of buprenorphine, which can be repeated approximately every 2 hours for one day (maximum daily dose of 12 to 16 mg on day 1, with goal to get to 16 mg by day 2). An alternative strategy is to start with a 4mg dose, then repeat after 1 hour and again after 4 hours as needed to treat withdrawal symptoms (for total dose on day 1 of up to 12mg); dosing is then adjusted in 4mg increments on subsequent days as needed.

Practically, for initiation, clinicians can prescribe enough buprenorphine for 1 week at the anticipated dose (often buprenorphine-naloxone (Suboxone) 8-2 mg twice daily).

Low dose buprenorphine

Also known as the Bernese method or micro-dosing, this strategy, first published in 2010, uses small doses of buprenorphine that increase gradually while the patient continues to use their usual full-agonist opioid over a period of days.[93] This allows the buprenorphine to slowly displace the other opioid from opioid receptors to avoid the risk of precipitated withdrawal. After buprenorphine has saturated receptors,

then the other opioid is stopped or tapered quickly. Dosing strategies vary, such as those presented in the table below; some low-dose buprenorphine initiation protocols extend as long as two weeks, and there is no evidence supporting use of one low-dose buprenorphine initiation protocol over another. An additional resource is available from CA Bridge (qrco.de/lowdose)

Table 5: Low dose buprenorphine initiation strategies

Day	Buprenorphine dosing strategy 1[94]	Buprenorphine dosing strategy 2[95]	Usual full-agonist opioid
Day 1	0.5 mg daily	0.5 mg daily	Continue use
Day 2	0.5 mg twice daily	0.5 mg twice daily	Continue use
Day 3	1 mg twice daily	1 mg twice daily	Continue use
Day 4	2 mg twice daily	2 mg twice daily	Continue use
Day 5	3 mg twice daily	2 mg three times daily	Continue use
Day 6	4 mg twice daily	4 mg three times daily	Continue use
Day 7	12 mg daily	Provider discretion (typical daily doses 16 mg or more)	Stop full-agonist opioid*

* Full-agonist opioid may be tapered in some protocols rather than abruptly stopped.

This type of transition may be particularly appropriate for patients who have chronic pain (as this strategy does not require stopping their pain regimen) and patients who are able to follow complex instructions required for film splitting and daily dose changes.

The main challenge with the strategy is that the starting doses are small. Splitting the films can be difficult and require dexterity. Daily dose changes require patients to be able to track and monitor their medication regimen, and they must have patience to follow through with a protocol that might last up to two weeks.

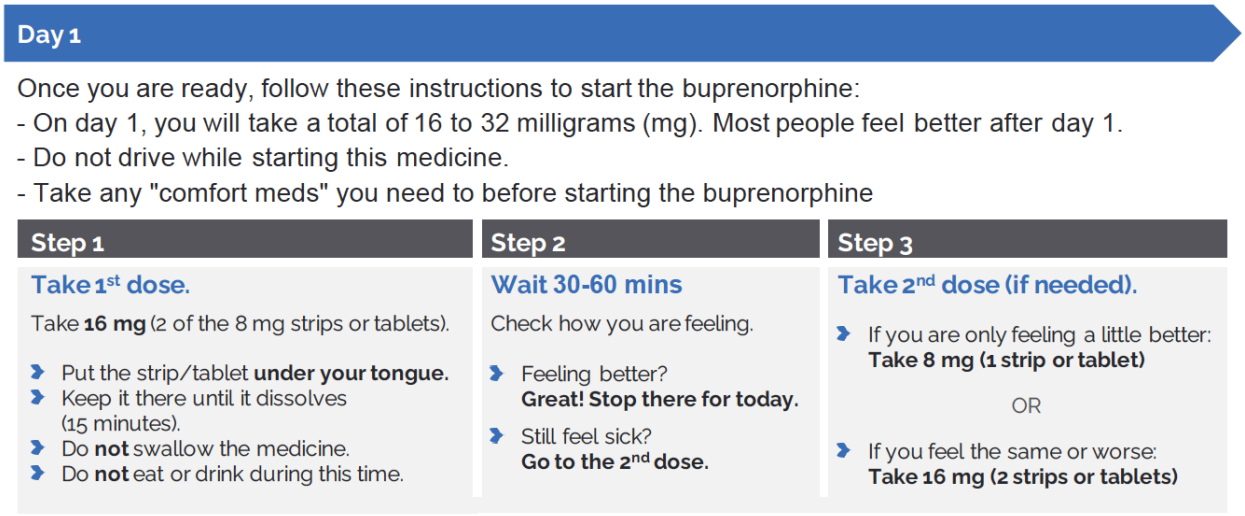
High dose buprenorphine initiation

This strategy, sometimes also called macro-dosing, uses high doses of buprenorphine (typically 16 to 32 mg) on day 1 to rapidly saturate opioid receptors. Patients are then transitioned to the maintenance dose, typically 16 mg depending on patient experience and opioid use patterns, on day 2.

When to start high dose buprenorphine depends on the setting. For patients who are initiating at home, withdrawal symptoms should be present. Severity of symptoms can be assessed with a formal tool (e.g., COWS), a count of withdrawal symptoms, or telling the patient to wait as long as they can after their last use to start – because the less full-agonist opioid in the patient's system, the smoother the process will be. The following medications to reduce withdrawal symptoms can help patients make the period before starting buprenorphine as long as possible:

- clonidine 0.1 mg three times daily PRN for anxiety/restlessness
- hydroxyzine 25-50 mg four times daily PRN for insomnia/anxiety
- ondansetron 4-8 mg by mouth three times daily PRN for nausea
- dicyclomine 10-20 mg by mouth every 6 hours PRN for abdominal cramping
- ibuprofen 400-800 mg by mouth every 6 hours PRN for muscle aches

Figure 13: Example for day 1 macrodose buprenorphine initiation



On **day 2** patients begin a 16 mg maintenance dose given once daily when convenient for them. This is continued until first follow-up.

Patients who do well with this type of transition are patients who have had an opioid overdose reversed in an acute care setting, who are unable to do a complex transition such as low dose buprenorphine initiation, or patients who are not willing to do the classic or standard buprenorphine initiation due to previous experience with precipitated withdrawal.

The challenge with this method is that it is still a relatively new process, so best practices are evolving.

Table 6: Summary of buprenorphine initiation strategies

Method†	Waiting period after last use until initiation	Duration of initiation	Withdrawal severity recommended at start of initiation	Medication taken during initiation phase	Expected change in withdrawal symptoms	Continued full agonist use during transition period	Time from initiation to treatment dose
Very Low-Dose "microdose"	None	Days to weeks	None	BUP-NX, initial dose <1 mg	N/A	Yes	Days to weeks
Low-Dose & Classic Dose	1-2 Days	1 day	Moderate	BUP-NX, initial dose 4 mg	Improve	No	1-3 Days
High-Dose "macrodose"	12 Hours	~2-3hrs	Moderate	BUP-NX, initial dose 16 mg	Improve	No	~15 Hours
QuickStart	None	~5 minutes	None	Intranasal naloxone, followed by 24 mg BUP-NX	Increased severity withdrawal for short duration, then improve	No	< 1 Hour

Initiating buprenorphine in emergency departments and via first responders

Coincident with the ongoing opioid crisis, emergency department visits for opioid overdoses, opioid withdrawal, and other complications of injection drug use have risen significantly.[96] Buprenorphine initiation for people with OUD presenting in EDs or via first responders, combined with linkage to appropriate outpatient care, may help reduce mortality and morbidity in this population.[97] Emerging evidence suggests that a relatively high-dose ED buprenorphine strategy (i.e., <12 mg sublingual) is safe and well tolerated in patients with untreated OUD.[97] Use of extended-release (i.e., 7-day) injectable buprenorphine may also be an effective strategy in ED settings.

ED initiation of buprenorphine can effectively engage patients in formal addiction treatment. A nonrandomized trial of this approach in 100 adults with OUD found low rates of precipitated withdrawal with 73% of patients engaged in OUD treatment after 7 days.[98] (Protocols for the use of buprenorphine in EDs are available at Bridgetotreatment.org.)

Consensus recommendations on the treatment of OUD in EDs by the American College of Emergency Physicians include:[96]

- Assessing for OUD using DSM-5 criteria
- Assessing for degree of opioid withdrawal using the Clinical Opiate Withdrawal Scale
- Assessing for pregnancy
- Offering treatment with buprenorphine in the ED (at least 8 mg buprenorphine for patients in withdrawal, with option to increase to 24 mg) or via prescription for home induction
- Discharge with a buprenorphine prescription sufficient to allow time for the patient to engage with an outpatient treatment program
- Use of harm reduction strategies including overdose education and naloxone distribution

Although initiation of buprenorphine is considered best-practice in ED settings[99] the use of methadone may also be effective, and may be preferred for patients who have been unsuccessful in the past with buprenorphine or who are at higher risk of treatment dropout. ED physicians may utilize the "72-hour rule" (an exception to the federal rule requiring that methadone for OUD only be provided in OTPs) to administer and initiate methadone for up to 3 consecutive days while arranging referral to treatment.[99] The evidence base to date for the use of methadone in EDs is limited to case series or reports,[99-101] so larger and more rigorous studies of this strategy are needed.

As outlined in the 2024 National Drug Control Strategy, treatment of OUD in an emergency department setting should follow a “cascade of care model” that includes follow-up for ED treatment for substance within 7 days, with another follow-up within 30 days.[102,103]

Maintenance dosing

Regardless of initiation approach, clinicians should schedule a follow up visit in 1 week but have someone from their team available by phone in the 1-2 days during initiation in case any problems arise.

A stable dose of buprenorphine reduces illicit opioid use, decreases cravings, and minimizes side effects. The buprenorphine dose may need to be adjusted to achieve these goals during this phase. The typical stabilization dose range is 12 to 24 mg daily sublingual buprenorphine. This occurs in the days to few weeks following initiation with buprenorphine.[104] Increasing the dose to 32 mg may be an option based on a patient’s response to treatment. The length of the maintenance phase is tailored to each patient and could be indefinite due to the high risk of relapse.

BOTTOM LINE: With the advent of fentanyl as the primary opioid of misuse, there has been an evolution in approaches to start patients on buprenorphine – in hopes of avoiding or minimizing precipitated withdrawal. Whether low dose, classic/standard dose, or high dose initiation, different methods to start buprenorphine have the potential to engage more patients in treatment.

Misconceptions about OUD treatment

Stigma and misunderstanding surround addiction generally and OUD in particular.[13] These include counterproductive ideologies that portray addiction as a failure of will or a moral weakness, as opposed to understanding OUD as a chronic disease of the brain requiring medical management that is no different from managing other chronic diseases such as diabetes or hypothyroidism. Some stigma and misunderstanding may persist due to the lack of awareness about how MOUD has evolved in the past 15 years.[105] Table 6 summarizes some common misconceptions about OUD and the corresponding realities.

Table 7: OUD treatment: Misconceptions vs. realities[12]

Misconceptions	Reality
Buprenorphine treatment is more dangerous than other chronic disease management.	Buprenorphine treatment is less risky than many other routine treatments, such as titrating insulin or starting anticoagulation, and easier to administer. It is also safer than prescribing full opioid agonists (e.g., oxycodone, morphine).
Using methadone or buprenorphine is simply "replacing one addiction for another."	Addiction is compulsive use of a drug despite harm. When taken as prescribed, methadone and buprenorphine improve function, autonomy, and quality of life; patients using these drugs do not meet the definition of addiction. Physical dependence is not the same as addiction.
Detoxification for OUD is effective treatment.	No data show that detoxification programs are effective for OUD, and, in fact, such interventions may increase the risk of overdose death by eliminating tolerance.
Prescribing buprenorphine is time consuming and burdensome.	Buprenorphine treatment can be readily managed in a primary care setting. In-office initiation or intensive behavioral therapy are not required for effective treatment.
If a patient returns to use, this is a treatment failure.	As with other chronic diseases (where behavior change takes time and isn't unidirectional), return to use is an expected occurrence in the course of substance use disorder. The goal of OUD treatment is to prevent acute and chronic complications (e.g., overdose or infection) and improve functionality and well-being. If a patient returns to use, care should be focused on meeting them with compassion, readdressing their goals, and resuming or revising their care plan.

Addressing stigma

Much stigma persists among health care professionals and some recovery communities toward people with OUD and medications used to treat OUD.[13] A 2016 national opinion survey (n=264) found that 54% of respondents thought people with OUD were to blame for their disorder, 46% felt such people were irresponsible, and 45% said they would be unwilling to work closely with such people.[106] A 2014 survey of 1,010 primary care physicians found similar, or even higher, levels of stigma related to people with OUD (depending on which specific statement was being compared).[107] Interviews with patients using methadone for OUD also suggest that this group experiences high rates of stigma and discrimination in

interactions with the public and with health care professionals,[108] which erodes their psychological well-being and may deter them from seeking treatment.[13]

Health care professionals can combat stigma by examining their own attitudes and beliefs and by consciously and consistently using neutral, "person-first," and non-stigmatizing language. Feeling stigmatized reduces patients' willingness to engage in treatment, and negatively influences clinicians' perceptions of people with OUD.[109]

Table 8: Alternatives to stigma-reinforcing words and phrases[109]

Avoid these terms	Use these instead
Addict, user, drug abuser, junkie	Person with opioid use disorder or person with opioid use disorder, patient
Addicted baby	Baby born with neonatal withdrawal syndrome
Opioid abuse or opioid dependence	Opioid use disorder
Problem	Disease
Habit	Behavior
Clean or dirty urine test	Negative or positive urine drug screen
Opioid substitution or replacement therapy	Medication for opioid use disorder
Treatment failure	Treatment attempt, return to use
Being clean	Being in remission or recovery
Medication-Assisted Treatment	Medication treatment for OUD (MOUD)

Here are some tips for creating an inclusive, non-stigmatizing medical practice:[24]

- Conduct a "language audit" of existing clinic materials for language that may be stigmatizing, then replace with more inclusive, person-first language.
- Critically reflect on the types of information you choose to disseminate to ensure that you are doing so responsibly.
- Every time you develop a prevention message, consider it an opportunity to dispel myths and convey respect.
- When developing new materials, seek input from various stakeholders, including people who use drugs and those with lived experiences.
- Train staff on issues related to substance use and stigma.

BOTTOM LINE: Stigma about OUD and medications to manage it persist among some clinicians and recovery communities. Stigmatizing words and behaviors can be reduced by choosing person-first language and taking steps to make practice settings more inclusive and welcoming.

Deregulation of buprenorphine prescribing

> *"Buprenorphine treatment provides one of the rare opportunities in primary care to see dramatic clinical improvement: it's hard to imagine a more satisfying clinical experience than helping a patient escape the cycle of active addiction."* --Sarah Wakeman, M.D., a practicing primary care physician in the Boston area

Due to historic regulations dating back to the Harrison Narcotic Act of 1914, prescribers have historically been prevented from prescribing opioids such as buprenorphine for patients with OUD. Until very recently, prescribers with a Drug Enforcement Administration (DEA) license needed to obtain a waiver (nicknamed the "X-waiver") to prescribe buprenorphine to treat OUD, which included educational requirements and limitations on the number of patients that could be treated. This waiver process restricted access to this life-saving therapy and perpetuated stigma associated with OUD.[110,111] In January 2023 this waiver process was eliminated. As a result, all clinicians authorized by the DEA and their states to prescribe Schedule III medications may now prescribe buprenorphine for OUD.[42] This regulatory loosening reflects the accumulated evidence that buprenorphine is safe, effective, and lowers rates of acute care services and associated costs.

BOTTOM LINE: Prescribing buprenorphine can broaden access to life-saving and life-enhancing treatment for OUD, and can be professionally satisfying for clinicians.

Harm reduction

Harm reduction is an approach that aims to reduce negative consequences associated with drug use. Harm reduction aligns with the goal of care for many chronic diseases: to prevent acute and chronic complications and improve functionality and wellbeing. Importantly, harm reduction does not require abstinence. Thus, the harm reduction approach broadens the scope of what primary care clinicians can offer their patients who use drugs and provides effective interventions for patients who do not want or are not ready for abstinence. As reviewed below, harm reduction is evidenced-based, effective, and safe.

Notably, a harm reduction approach is applicable to other areas of public health and primary care – other examples include seatbelts to reduce harm from driving, sunscreen to prevent harm from sun exposure, or condoms to reduce transmission of sexually transmitted infections.

Opioid reversal prescription and education

Naloxone (e.g., Narcan) and nalmefene (Opvee), opioid antagonists, immediately reverse the effects of opioids. One of these medications should be prescribed to any patient who is prescribed or uses opioids, particularly those taking >50 morphine milligram equivalents per day, with comorbid cardiopulmonary disease, or use of other prescribed or nonprescribed sedating substances (e.g., benzodiazepines). Naloxone should also be prescribed for patients using other illicit substances given risk of contamination with synthetic opioids.[112] Communities that had overdose education and naloxone distribution for people using opioids, social services staff, and family/friends of people using opioids, had significantly reduced opioid related overdose death rates.[113]

Medications for OUD

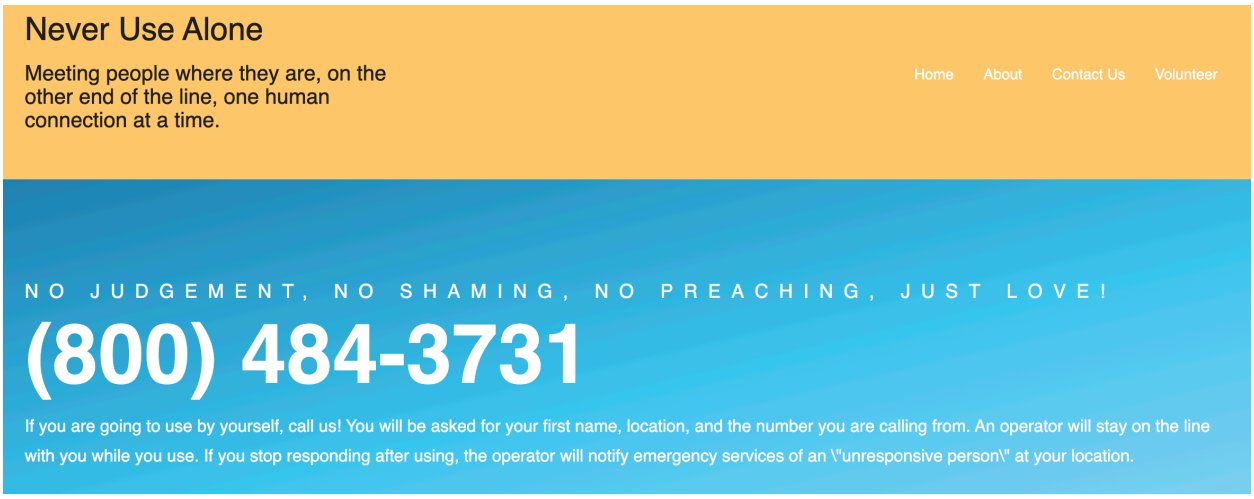
As described previously, medications for OUD (particularly buprenorphine and methadone) are extremely effective in preventing opioid overdose. Importantly, these medications prevent overdose even if patients continue to use additional opioids. Therefore, medications for OUD should never be discontinued because a patient returns to use.

Testing for fentanyl

The illicit drug supply is unregulated and may be marketed as one substance but be contaminated with synthetic opioids such as fentanyl. Therefore, offering fentanyl test strips empowers patients to test their substance to evaluate the risk of overdose.[114] With this knowledge, they can take steps such as ensuring they do not use alone or taking a test dose, to prevent overdose.

Reducing risk of using alone

Solo use of opioids may increase the risk of death from overdose. Clinicians can offer patients resources such as the “Never Use Alone” hotline that patients can call; if the patient stops responding to the operator while/after using, the operator will call emergency services.



Preventing infections

Intravenous drug use and to a lesser extent inhalation drug use are associated with increased risk for bacterial and viral infections. Certain use practices such as sharing injection or smoking supplies place patients at greater risk. It is the primary care clinician’s role to 1) screen for these infectious diseases and 2) discuss ways to prevent these infections.

Screening for infectious complications

In addition to bacterial infections such as syphilis and skin and soft tissue infections, patients who use drugs are at increased risk for blood-borne pathogens such as HIV, Hepatitis C, and Hepatitis B. Patients should be screened for syphilis and other sexually-transmitted infections at least annually, and more frequently if they have many potential exposures.

Preventing infectious complications

Ensuring patients have access to sterile supplies is one of the best ways to prevent infections. Syringe exchange programs distribute sterile supplies and safely dispose of used supplies. One systematic review of 15 studies analyzing syringe exchange programs found that they are associated with decreased prevalence and incidence of HIV and HCV.[115] Information regarding syringe exchange program locations can be found at nasen.org. If no syringe exchange program is available locally, primary care clinicians can prescribe insulin syringes that patients can pick up at their pharmacy.

Pre-Exposure HIV Prophylaxis (PrEP)

PrEP is taking an antiretroviral medication to prevent HIV infection. This is usually a once-daily pill (Truvada or its generic, Descovy); there is also a long-acting injection (Apretude). PrEP is indicated for people who inject drugs and are at risk of HIV, such as those who share injection equipment with others, and patients who are also sexually active, especially if the patent engages in transactional sex.[116] Primary care clinicians can inform patients about the availability of PrEP, and offer it if patients are interested.

Special populations

Treating acute pain in patients on medication for OUD

Some clinicians may not prescribe effective opioid analgesia to manage acute pain for patients with OUD who are using methadone or buprenorphine due to concerns about respiratory depression, overdose, or diversion. As a result, this population is at particular risk of under-treatment for acute pain.

Clinicians may also mistakenly assume that acute pain is adequately controlled with the long-term opioid agonist (i.e., methadone) or partial agonist (i.e., buprenorphine). These medications are treating the patient's OUD, allowing patients to feel normal; therefore, acute pain should be treated separately. Notably, methadone and buprenorphine have an analgesic duration of action (four to eight hours) that is substantially shorter than their suppression of opioid withdrawal (24 to 48 hours).[117] In addition to other methods of pain management, it can therefore be helpful to divide the total daily dose of buprenorphine into a dose every 6-8 hours. However, in general, it is inadequate to solely rely on a patient's maintenance methadone or buprenorphine dose to provide analgesia for acute pain.

Non-opioid analgesics (e.g., acetaminophen and NSAIDs) are first-line options for treating acute pain in this population. For moderate-to-severe pain not adequately controlled with non-opioids, however, use of opioid analgesics should be considered. Importantly, patients taking methadone or buprenorphine generally have a high cross-tolerance for analgesia, leading to shorter durations of analgesic effects. Higher opioid doses administered at shorter intervals are likely necessary for adequate pain control.

Since ER naltrexone will block the effects of any opioid analgesics, acute pain in such patients (e.g., that associated with dental work, surgery, or traumatic injury) should be treated with regional analgesia, conscious sedation, non-opioid analgesics, or general anesthesia.[24] Attempting to overcome the opioid blockade with high doses of opioids increases the risk for overdose.[118]

If opioids are deemed necessary for patients on methadone or buprenorphine, clinicians should verify the patient's methadone or buprenorphine dose, and ensure that an overdose reversal agent is available. Clinicians should inform the program or prescribing healthcare professional about the addition of new

opioids (or any other controlled substance), as this may affect subsequent toxicology screen results. As with any patient, it can be helpful to set expectations upfront that we may not achieve "zero pain" but, will strive for a level of analgesia that maximizes a patient's physical and mental functioning.[119]

BOTTOM LINE: Patients with acute pain whose OUD is managed using methadone or buprenorphine are at risk for under-treatment of pain. Non-opioid analgesics (oral or topical) are recommended as first-line agents, but additional opioids may be warranted for moderate to severe pain.

Pregnancy and OUD

We acknowledge that people who do not identify as women can also become pregnant. Studies on OUD and pregnancy are mostly in cis-gendered women.

The prevalence of OUD among pregnant women, while low in absolute terms, quadrupled from 0.15% in 1999 to 0.65% in 2014, with large variability across states.[120] Overdose is one of the leading causes of maternal deaths in the U.S., with the rate of overdose lowest in the third trimester (at 3.3/100,000 person-days) and highest 7 to 12 months after delivery (12.3/100,000 person-days).[121] Pregnant women with untreated OUD have up to six times more maternal complications than women without OUD, including low birth weight and fetal distress, while neonatal complications among babies born to mothers with OUD range from neonatal opioid withdrawal syndrome and neurobehavioral problems to a 74-fold increase in sudden infant death syndrome.[122]

Both methadone and buprenorphine are recommended for treating OUD in pregnancy to improve outcomes for both mother and newborn.[13] The efficacy and safety of methadone treatment for OUD in pregnant women was established in the 1980s, showing that maternal and neonatal outcomes in women on methadone treatment during pregnancy are similar to women and infants not exposed to methadone.[123]

More recent research suggests that buprenorphine treatment also has benefits in this population. A randomized controlled trial including 175 pregnant women with OUD found that neonates of women on buprenorphine required 89% less morphine, had shorter hospital stays, and received a shorter duration of treatment for neonatal abstinence syndrome compared to neonates of those treated with methadone.[124] Other outcomes and adverse events were similar between the two groups. Although some treatment programs switch pregnant women to buprenorphine monotherapy to avoid naloxone crossing the placenta and adversely affecting fetal growth, no evidence exists for harm from using the combination product and some experts now recommend that all pregnant women continue on buprenorphine/naloxone rather than switch temporarily to buprenorphine monotherapy.[125]

The safety of ER naltrexone has not yet been established for pregnant women, and naltrexone is not recommended for the treatment of OUD in pregnant women.[13] Naloxone in life-threatening emergencies is recommended.

Despite data supporting medication use, most pregnant women with OUD do not receive any treatment.[126] Among those who do, many fall out of treatment during the post-partum period due to gaps in insurance coverage and other systemic barriers. An integrated approach with close collaboration between OUD treatment providers and prenatal providers has been described as the "gold standard" for care, and further research is needed to investigate interventions that could help to increase treatment retention.[13]

BOTTOM LINE: Both methadone and buprenorphine (with or without naloxone) should be used to treat OUD in pregnancy to improve outcomes for both mother and newborn.

Walking the road of recovery

As with other chronic diseases such as asthma or diabetes, the goal of treatment for OUD is not so much a "cure" as improved and sustained functioning in all spheres of life. Addictions such as OUD *can* be managed successfully. Treatment enables people to counteract addiction's disruptive effects on their brain and behavior and regain control of their lives.[127]

The chronic nature of addiction means that for some patients, relapse is an expected part of the overall trajectory of recovery, particularly if they stop following their treatment plan or medications.[127] Relapse rates for drug use are similar to rates of relapse for patients treated for hypertension or asthma.[128] Treating chronic disease states involves changing deeply-rooted behaviors and relapse doesn't mean treatment has failed—it should be interpreted as a need to work with the patient to resume or modify the management plan.

Recovery is also a multi-dimensional process, with medical management being a necessary, but typically not sufficient, component. Four major life dimensions play vital roles in recovery from any addiction or disease state:[129]

- Health: overcoming or managing one's disease(s) or symptoms and making healthy choices that support physical and emotional well-being
- Home: having a stable and safe place to live
- Purpose: having meaningful daily activities or work and having the independence, income, and resources to participate in society
- Community: having relationships and social networks that provide emotional support

Clinical support of recovery requires flexible, personalized approaches that are responsive and respectful of the diversity of patient beliefs, practices, cultural needs, and life situations. What may work for one person may be ineffective for another, and each person will have a unique constellation of needs and challenges that can be met with an equally unique array of support personnel and structures. Incorporating peer support (e.g., people with personal experience with substance use or substance disorders), either formally or informally, in the treatment process may facilitate recovery and improve chances for treatment adherence.[79,130]

BOTTOM LINE: OUD can be managed successfully. Return to opioid use while on treatment is common and should not be viewed as a "failure," but instead as an opportunity to re-engage with a patient, check in about relevant aspects of their life, and adjust the management plan, if appropriate.

Putting it all together

Nearly 6 million people in the U.S. are estimated to have OUD, which is associated with a 20-fold greater risk of early death due to overdose, infectious diseases, trauma, and suicide.[12,13] Medications for OUD including methadone and buprenorphine work by alleviating withdrawal symptoms, reducing opioid cravings, improving treatment retention, and preventing overdose. These are some of the most effective and life-saving medications in medicine today. Importantly, these medications also help people improve their functionality and quality of life, and can allow them to reintegrate with their families, jobs, and communities.

This document has laid out the evidence supporting these conclusions and provides the basis for the following statements and recommendations:

- OUD is a chronic, treatable disease.
- Because of neurochemical changes in the brain caused by exposure to opioids, medication treatment is key to addressing OUD for many patients—counseling or behavioral therapies may not necessarily be required but are helpful adjuncts.
- Screen and manage all patients for opioid misuse using SBIRT (Screening, Brief Intervention, and Referral to Treatment).
- Initiate treatment for patients diagnosed with OUD with buprenorphine or connect patients to Outpatient Treatment Programs (OTPs) for methadone. If this is not possible due to patient preference or access barriers, initiate extended-release naltrexone therapy, except in the case of a planned or current pregnancy.
- Prescribe overdose-reversing agents, and ensure they are available to all patients with OUD and those who are at risk for experiencing or responding to an opioid overdose—they can be lifesaving.
- Using buprenorphine to treat people with OUD can be highly effective for the patients, and very satisfying for the treating clinician.

Appendix I: Reimbursement for SBIRT

Payer	Code	Description	Fee Schedule
Commercial Insurance	CPT 99408	Alcohol and/or substance abuse structured screening and brief intervention services; 15 to 30 minutes	$33.41
	CPT 99409	Alcohol and/or substance abuse structured screening and brief intervention services; greater than 30 minutes	$65.51
Medicare	G0396	Alcohol and/or substance abuse structured screening and brief intervention services; 15 to 30 minutes	$29.42
	G0397	Alcohol and/or substance abuse structured screening and brief intervention services; greater than 30 minutes	$57.69
Medicaid	H0049	Alcohol and/or drug screening	$24.00
	H0050	Alcohol and/or drug screening, brief intervention, per 15 minutes	$48.00

Source: samhsa.gov/sbirt/coding-reimbursement Accessed 6.24.2024

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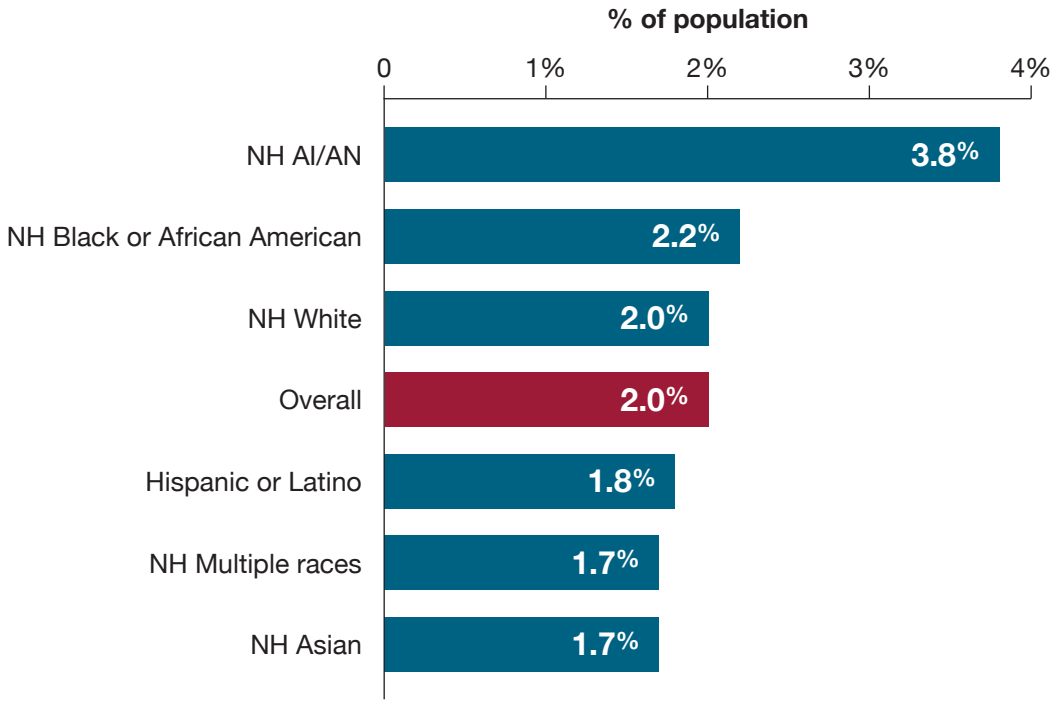
Appendix I: Managing opioid use disorder in the care of American Indians and Alaska Natives

Background

American Indian or Alaska Native (AI/AN) peoples have historically experienced disparities in access to healthcare services, funding, quality and quantity of services, health education, and prevention services relative to other groups.[1] AI/AN communities have also been particularly impacted by the ongoing epidemic of opioid use disorder (OUD) and opioid-related overdoses and death. In 2021 alone, 1,358 AI/AN persons died of an opioid overdose.[2] Among people aged 12 or older in 2022 (the latest year for which these data are available) the percentage who had a past year OUD was 3.8% among AI/AN people compared to 2% for White people, 2.2% for Black or African American people, and 1.7% for Asian people (Figure 1).[3] Similarly, rates of prescription pain reliever use disorder were highest among AI/AN people (3.9%) compared to other races/ethnicities.[4]

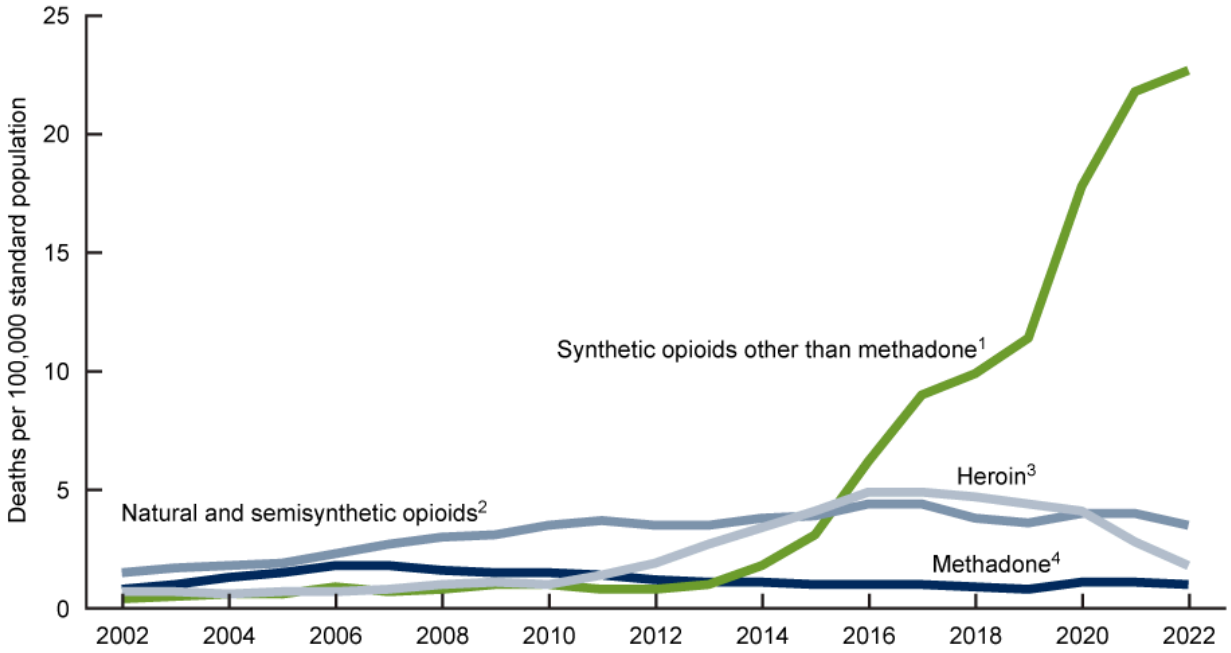
Figure 1: Opioid use disorder in adults age 12 and older by origin and race in 2023[5]



NH=Not Hispanic; AI/AN=American Indian/Alaska Native

These statistics occur against the backdrop of the wider crisis of opioid misuse and abuse. The Centers for Disease Control and Prevention estimated that in the 12 months ending in December, 2022, 105,452 people in the U.S. died from an opioid overdose, equating to 288 overdose deaths each day.[6]

Figure 2: Opioid-related overdose deaths by type in the U.S.[7]



Cultural aspects of prevention and recovery among AI/AN peoples

> We need to protect our people and our tribal communities from this disease. Protection starts with prevention. Culture is prevention. Strong families and communities are prevention. And education is prevention.
>
> *--Kailee Fretland, pharmacist, White Earth Nation Tribal Affiliation, Red Lake Service Unit, Indian Health Service.*[8]

The views of AI/AN communities about health, illness, and the prevention of, and recovery from, substance use, are diverse and reflect the variety of cultural backgrounds, traditions, and spiritual beliefs among the hundreds of recognized tribes. However, some shared perspectives can be identified and awareness of these perspectives can help inform more effective, empathic care:[1]

- Holistic approach. AI/AN peoples approached health and wellness from a holistic perspective long before this became more common in traditional medicine. AI/AN communities are more likely to view health as being a balance of physical, emotional, mental, and spiritual components and, thus, they might consider family and community relationships, spiritual practices, and connections with the land and ancestors as integral parts of wellness and recovery.
- Traditional healing practices. The use of medicinal plants, sweat lodges, smudging (burning of specific herbs for purification), and healing rituals may be part of an approach to managing SUDs in AI/AN communities. Such practices may not only relieve physical discomfort but may also help to restore balance and harmony within the individual and the community.
- Storytelling, dance, and art may play a role in helping to manage or overcome SUDs; they can serve as forms of expression, therapy, and connection to cultural history and community.

- Spiritual beliefs. Healing ceremonies led by spiritual leaders, elders, or medicine people may complement care from traditional (i.e., Western) medical providers in some AI/AN communities, and these should be respected and embraced.
- Historical trauma: The cumulative emotional and psychological wounding across generations due to mistreatment, genocide, and many other forms of cultural abuse against AI/AN people may play a role in creating conditions that increase the risk for substance use. Understanding and addressing this trauma can be a component of holistic SUD management strategies.

Health care providers working in the IHS systems are now working to incorporate these perspectives into their practice, recognizing the importance of culturally responsive care, integrating traditional practices where appropriate, and addressing the social determinants of health that disproportionately affect AI/AN communities. Health-related social needs, or social determinants of health (SDOH) include such things as food insecurity, housing instability, interpersonal violence, transportation limitations, and utility needs. Such concerns or issues must be addressed and supported as part of the larger context of substance use disorder treatment for each individual patient.

Figure 3: Helping ensure basic needs are met

Figure courtesy of Oregon Health Authority, www.bit.ly/OHA_HRSN

Consider screening for SDOH with one of these validated tools based on your practice's individual needs:

1. **Accountable Health Communities (AHC):** www.bit.ly/CMS_screen
2. **Health Leads Social Needs Screening Toolkit:** www.bit.ly/SN_screen
3. **American Academy of Family Physicians (AAFP) Social Needs Screening Tool:** www.bit.ly/2GTFFqz
4. **PCSS SUD 101 Core Curriculum (2023):** www.bit.ly/PCSS_SUD

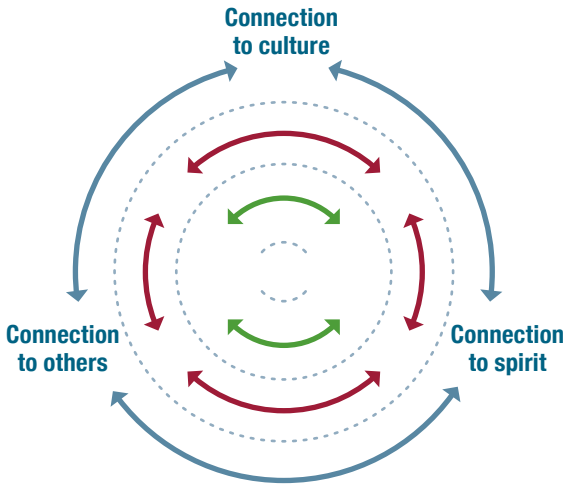
OUD treatment works, but is under-used

Strong evidence demonstrates that treatment with medications for OUD (MOUD) delivered by primary care clinicians or in specialized clinics can significantly reduce rates of death, overdose, and return to use in persons with OUD.[9,10] These evidence-based treatments, however, remain significantly under-used. Only about 22% of the 2.5 million people with OUD in the U.S. received MOUD treatment in 2021.[4] Access to MOUD treatment, as well as many other services for those with substance use disorders, can be limited for AI/AN people by a range of societal factors such as high levels of poverty (25.4% for AI/AN people vs. 13.4% of the general population), long distances to healthcare facilities, limited expertise in

SUD among healthcare providers, higher rates of trauma, and higher-than-average rates of certain physical problems such as diabetes and cardiovascular disease.

Entry to the path to recovery can occur at any time. Continuing to talk to patients about what they value and what motivates them will help engage them with recovery services. Recommendations and resources should be flexible and individualized. Peer navigators can be powerful resources to help connect patients with culture and community through recovery. The cascade of care model can be used in any setting to start the recovery journey. This model consists of four stages, or areas, of care that interact with one another: prevention, identification, treatment, and recovery.[11] As used in the context of OUD, the model emphasizes progressive stages treatment including engagement in care, initiation of MOUD, retention in treatment, and care in remission.

Figure 4: Engage patients with OUD in circle[12]



The primary Evidence Document, of which this is a supplement, summarizes current best practices for managing patients with OUD, presents the evidence supporting the use of MOUD, and makes recommendations for addressing the urgent needs for treatment, not just among the AI/AN population, but of the nation as a whole. The **Substance Use Warmline (1-855-300-3595)** offers free clinician-to-clinician support for IHS providers looking for expert recommendations on the evaluation and management of opioid, alcohol, and other substances of abuse. General information and a wealth of links to other resources can be found on the opioid stewardship pages of the IHS website (ihs.gov/opioids/recovery). Opioid overdose prevention is also a priority, and the federal Indian Health Manual includes specific recommendations for dispensing the overdose-reversing agent Naloxone to first responders and community representatives.[13]

OUD treatment works, but is under-used

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These are general recommendations only; specific clinical decisions should be made by the treating clinician based on an individual patient's clinical condition.

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