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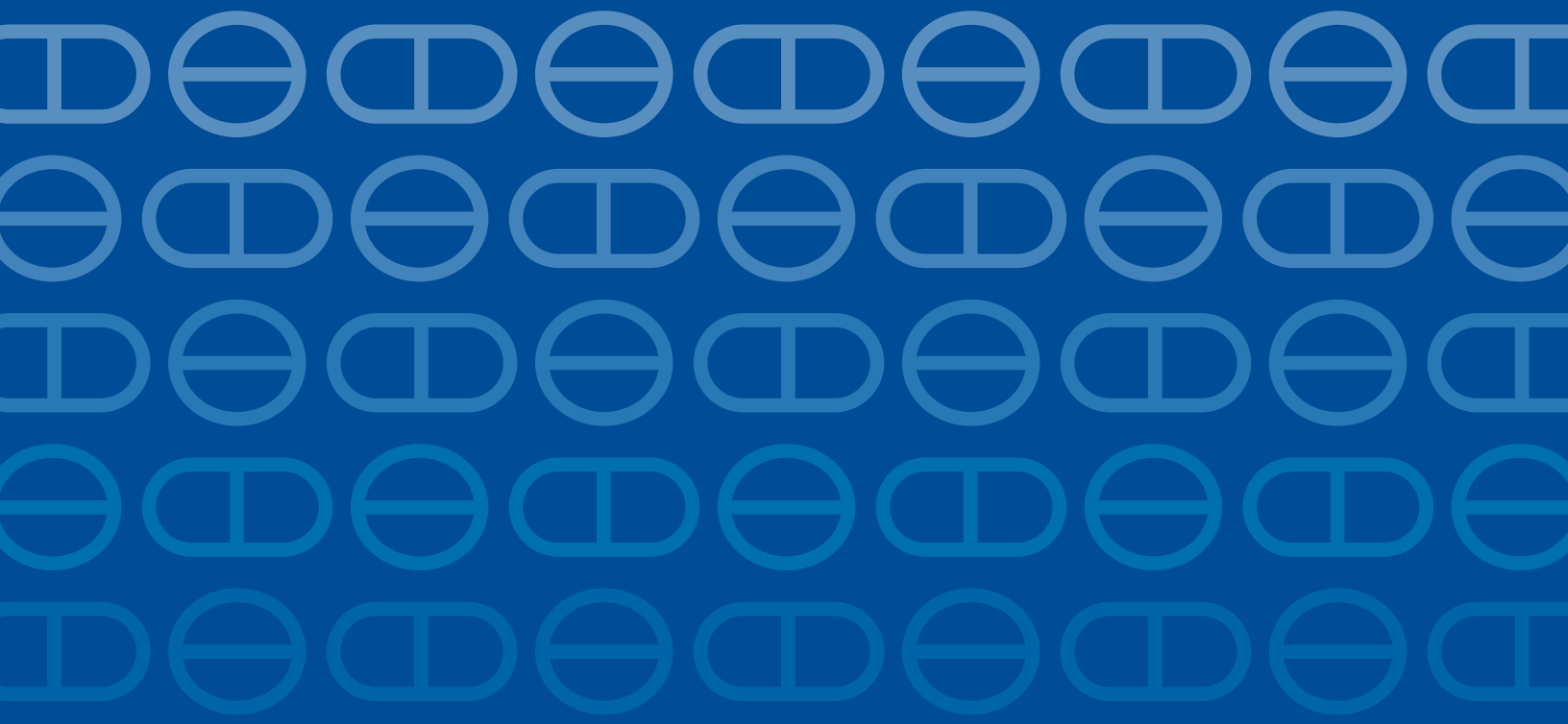
Management of opioid use disorder in primary care



Management of opioid use disorder in primary care

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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.

Alosa Health

Management of opioid use disorder in primary care

Activity Start Date: August 1, 2022
Activity Termination Date: July 31, 2025

This activity offers CE credit for:

1. Medicine (AMA)
2. Nurses (ANCC)
3. Pharmacists (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 primary care setting, to educate clinicians about the diagnosis and evidence-based treatment of OUD with medications, and to encourage clinicians to obtain the education necessary 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 OUD and initiate treatment using SBIRT: Screening, Brief Intervention, and Referral to Treatment
- Utilize the *DSM-5-TR* diagnostic criteria for 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
- Review the requirements for an X-waiver to prescribe buprenorphine for the indication of OUD
- 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, nurse practitioners, physician assistants, nurses, pharmacists 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 1.5 *AMA PRA Category 1 Credit(s)™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Nurses: This activity is designated for 1.5 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.

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Pharmacists (ACPE): This knowledge-based activity is approved for 1.5 contact hours (0.15 CEUs) of continuing pharmacy credit (UAN JA0007185-9999-22-110-H08-P).

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Susan Yarbrough, CHCP is the Senior Director of Educational Excellence at CME Outfitters, LLC. Ms. Yarbrough has no relevant financial relationships to disclose.

Scott J. Hershman, MD, FACEHP, CHCP has nothing to disclose.

Disclosures were obtained from the CME Outfitters, LLC staff: Nothing to disclose.

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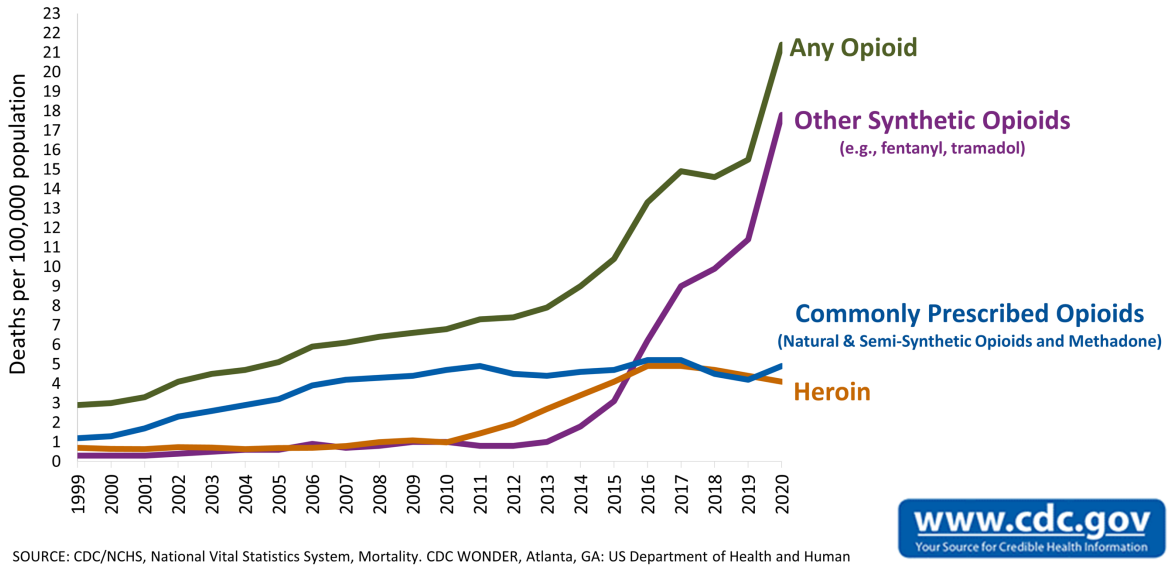
Table of Contents

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 2021, the CDC estimated that nearly 100,000 people in the U.S. died from an opioid overdoses, equating to 277 overdose deaths each day.[3,4] 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.[5]

Figure 1: Opioid-related overdose deaths by type in the U.S.[6]



SOURCE: CDC/NCHS, National Vital Statistics System, Mortality. CDC WONDER, Atlanta, GA: US Department of Health and Human Services, CDC; 2020. https://wonder.cdc.gov/.

The rise in opioid overdose deaths is related to dramatic increases in the number of persons misusing opioids (i.e., use of opioids other than as prescribed). In 2020, approximately 9.3 million Americans aged ≥12 years reported that they misused prescription opioids in the past year.[7] Among these, 2.7 million people met the criteria for opioid use disorder (OUD).

These alarming statistics persist despite strong evidence that treatment with medications delivered by primary care clinicians or in specialized clinics can significantly reduce rates of death, overdose, and return to use in persons with OUD.[8,9] These evidence-based treatments, however, remain vastly under-used. Only about 1 in 10 people with OUD receive medication as treatment.[10] Access to treatment is a major barrier. The number of clinicians authorized to provide these treatments remains inadequate; in 2017, more than half of U.S. counties with no buprenorphine prescriber.[8,11] Additionally, the opioid epidemic has disproportionately impacted non-Hispanic Black, American Indian/Native Alaskan, and Hispanic communities, which are less likely to have access to and be offered treatment despite having similar rates of OUD.[12] This report summarizes the current evidence supporting the use of medication to

manage OUD and makes recommendations for addressing the needs of this under-recognized, and often stigmatized, population.

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).

BOTTOM LINE: Opioid misuse is a serious problem in the U.S., claiming approximately 277 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 neurocircuitry involved in the development of substance use disorders is well-described[13,14] and critical for understanding how 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.[15-17] Many people with OUD, or who misuse opioids (i.e., 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), obtain opioids via a valid prescription (36.1%) or from friends and relatives (53.1%).[18] Both OUD and opioid misuse are associated with intentional and unintentional opioid-related overdose events.[19]

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:[20]

- 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

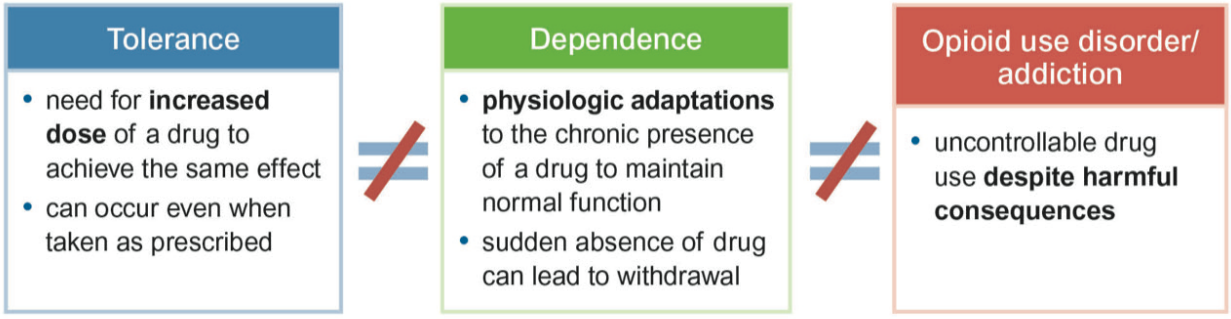
- recurrent opioid use in hazardous situations (e.g., driving)
- continued use despite a physical or psychological problem caused by or worsened by opioid use
- tolerance (unless opioids are being taken as prescribed)
- using opioids to prevent withdrawal symptoms (unless opioids are being taken as prescribed)

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)

Notably, opioid dependence is not the same as opioid use disorder (or addiction). Physical 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 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 and opioid addiction involves cravings, lack of control, and recurrent use after withdrawal. Additionally, physical 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 opioid addiction stigmatizes the medications used to treat OUD such as buprenorphine.

Figure 2: Opioid dependence does not equal opioid use disorder[21]



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. Opioid use disorder 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 that is used to facilitate screening patients for OUD.[22] SBIRT typically takes 5-10 minutes to administer and has been endorsed by the Substance Abuse and Mental Health Services Administration (SAMHSA).[23] Note that clinicians can be reimbursed for following the SBIRT process.

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.[23]

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 substances and patterns of use. This can be done with an informal conversation or formal screening tools.

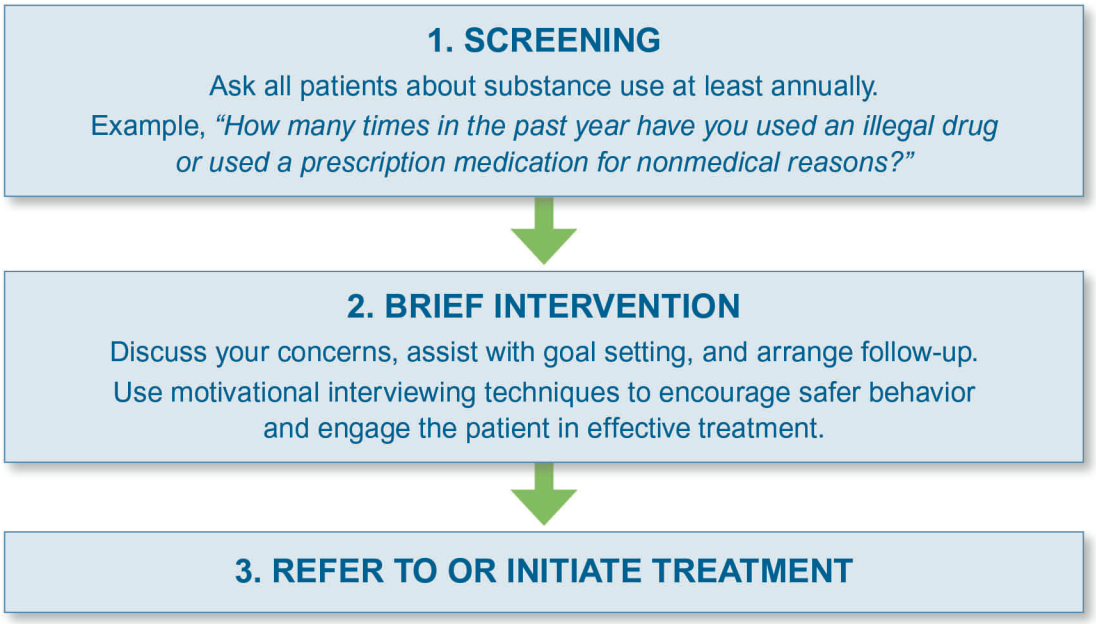
More comprehensive tools to screen for substance use screening include:

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

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 naloxone rescue access (e.g., nasal Narcan).
- ***Arrange*** follow-up appointments, either in person or by telehealth.

Figure 3: 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.

Medications to treat OUD

The U.S. Food and Drug Administration (FDA) has approved three medications for treating OUD: buprenorphine, methadone, or extended-release (intramuscular) naltrexone. All three medications can reduce cravings for and misuse of opioids.[9] However, extended-release (ER) naltrexone is considered a "second-line" medication due to difficulty with induction (patient needs to go 7-10 days without opioids prior to receiving ER naltrexone) and inferior overdose reduction effects compared to methadone and buprenorphine.[24,25] 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[9]

Medication	Dosage form	Product name
Buprenorphine	Sublingual tablet	Subutex, generics
	Subcutaneous injection (extended release)	Sublocade
	Subdermal implant	Probuphine (now off the market and only available to previous maintenance patients)
Buprenorphine/naloxone	Buccal film	Bunavail, 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-releases naltrexone.		

Methadone

Methadone is a synthetic, long-acting, full agonist at mu-opioid receptors.[26] This activity reduces the unpleasant/dysphoric symptoms of opioid withdrawal (please see page 23 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. Note that methadone can be provided when patients are admitted to a hospital for treatment of other conditions or in emergencies.[27] New patients are required to visit a methadone clinic every day to receive their dose. Eventually, stable patients may receive take-home doses if they meet certain criteria, such as having a stable period of good functioning without illicit drug use.[23] In addition, patients on methadone are usually required to attend regular counseling sessions with clinic providers.

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,[28] but that risk is significantly lower compared to people who are not in treatment.[29,30]

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

Methadone can induce respiratory depression, particularly when combined with benzodiazepines or other central nervous system (CNS) depressants. However, the FDA advises that methadone not be withheld from patients taking benzodiazepines or other central nervous system (CNS) depressants because the risk of overdose is even higher among OUD patients not on methadone.[31] The other potential harms of methadone include hypogonadism, which is a common side effect of chronic use of any opioid, and QTc segment prolongation. QTc segment prolongation may be monitored at least annually or after dose increases. 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 for patients receiving methadone maintenance.[26]

Buprenorphine

Buprenorphine is a high-affinity, partial agonist at mu-opioid receptors as well as an antagonist at the kappa and delta opioid receptors.[32] 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,[33] and a therapeutic dose may be achieved within a few days.[34] The risk of opioid overdose declines immediately when patients with OUD initiate buprenorphine treatment.[30]

Buprenorphine undergoes extensive first-pass metabolism in the liver and therefore has very low oral bioavailability.[35] 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. Some formulations of buprenorphine are only FDA-approved to treat pain and not OUD, including buprenorphine-only patch (Butrans) and buprenorphine-only film (Belbuca).

All formulations of buprenorphine decrease opioid misuse, reduce risk of overdose, and increase negative urine drug screens compared to no treatment.[36] Some formulations require patients be stabilized on transmucosal buprenorphine prior to initiation (i.e., subcutaneous injection).

Buprenorphine can be prescribed in a primary care setting to patients, and patients can take their prescription to be filled at the pharmacy for self-administration. In order to prescribe buprenorphine, eligible clinicians in the U.S. must apply for a waiver (informally called an X-waiver) from the Drug Enforcement Administration (DEA) which is added to their independent DEA license for controlled substance prescribing privileges (for details see "Obtaining an X-waiver" section below). If a practitioner wants to prescribe buprenorphine for OUD for more than 30 patients concurrently, they must also complete a training course (usually an 8-hour approved course for physicians). Nurse practitioners (NPs) and physician assistants (PAs) may also obtain X-waivers since the Comprehensive Addiction and Recovery Act of 2016. The Substance Use-Disorder Prevention that Promotes Opioid Recovery and Treatment for Patients and Communities Act (SUPPORT Act) of 2018 expanded authorization to certified nurse specialists, certified registered nurse anesthetists, and certified nurse midwives. For non-physician clinicians, the required training if prescribing buprenorphine for more than 30 patients concurrently is 24 hours.[37]

Similar to methadone, buprenorphine sustains opioid tolerance and physiological dependence in patients, so discontinuation can result in withdrawal—although buprenorphine's withdrawal syndrome may be less severe compared to methadone. The most common side effects are constipation, vomiting, headache, sweating, insomnia, and blurred vision. The risk of hypogonadism is lower with buprenorphine compared to methadone, and buprenorphine is not associated with QTc prolongation or cardiac arrhythmias.[38]

One risk of buprenorphine (as well as naltrexone) is 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.[9] Thus, in a standard buprenorphine initiation, a patient must be in mild to moderate opioid withdrawal prior to initiation to avoid exacerbating the withdrawal. An alternative buprenorphine initiation strategy (informally referred to as "microdosing") introduces low-dose buprenorphine while a patient is still using full opioid agonists, with slow increases in buprenorphine until a threshold dose is achieved and a patient can discontinue their full opioid agonist.[39]

Buprenorphine has very few clinically significant drug interactions, with common exceptions being delavirdine, atazanavir, and rifampin.[40] Comparative efficacy data on different buprenorphine formulations are limited. A randomized trial comparing buprenorphine implant to sublingual buprenorphine found higher levels of negative urine screens and abstinence with the implant, but the differences did not reach statistical significance.[41]

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.[32] 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.[9]

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 using methadone or buprenorphine substitution can be followed by a 7 to 10 day waiting period before beginning naltrexone; non-opioid detoxification (such as with clonidine or lofexidine) can be used during the 7 to 10 day waiting period from entry into detoxification treatment. This process can be a very significant barrier to naltrexone stabilization because of the high risk for opioid relapse and/or drop out from care as the patient endures opioid withdrawal symptoms.[9] Strategies to support 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.[42]

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 OUD.[43-46]

Naloxone vs. Naltrexone: What's the difference?

Naloxone (Narcan) is an opioid antagonist given by injection or nasal spray to reverse overdoses. It acts within minutes and lasts for only about an hour due to rapid metabolism.

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 suggests 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.[9,34] The evidence base for ER naltrexone is less robust than for methadone or buprenorphine.[9] The outcomes used to demonstrate efficacy vary between studies and include: decreased illicit opioid use (often measured by urine drug testing), treatment retention rate, drug-related overdose deaths, self-reported use and cravings, and all-cause mortality.

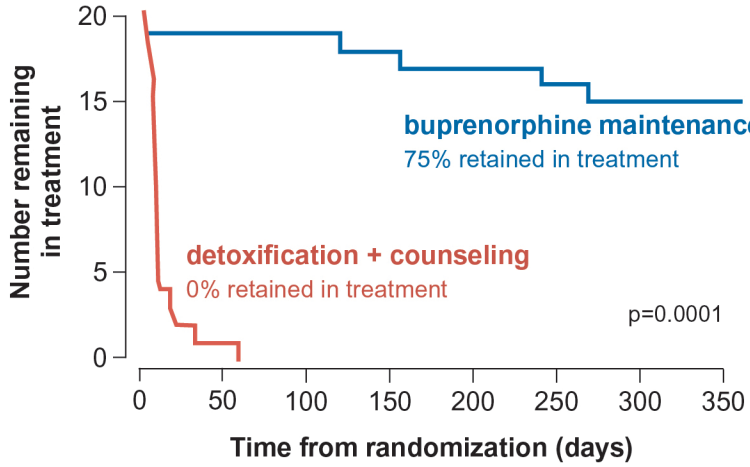
As demonstrated by the data below, people with OUD treated with methadone or buprenorphine are less likely to die, less likely to overdose, and more likely to remain in treatment. Using medication to treat OUD is also associated with improved social functioning and quality of life compared to people not on medications.[23]

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).[47] 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.

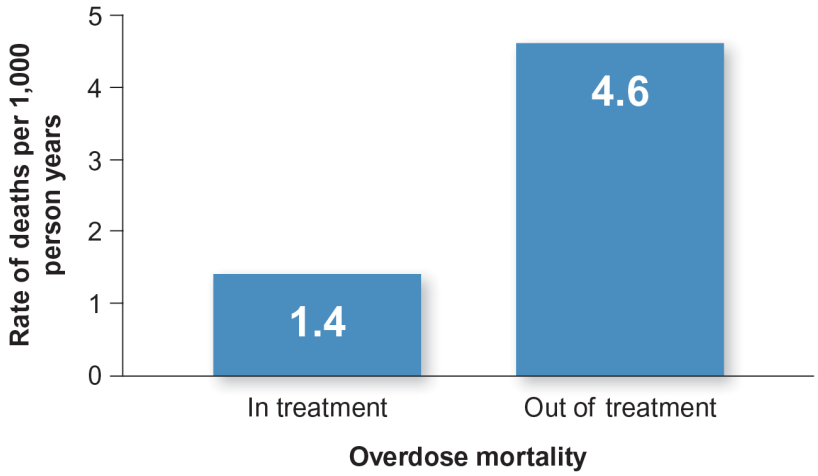
A small trial in Sweden randomized 40 adults with OUD to daily buprenorphine 16 mg sublingually for one year vs. a six-day taper of buprenorphine followed by placebo.[48] After one year, 75% of patients on buprenorphine remained in treatment and were abstinent vs. 0% in the placebo group, and 20% of those in the placebo group died. No deaths occurred in the buprenorphine group.

Figure 4: Buprenorphine associated with improved treatment retention[48]



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).[30]

Figure 5: Increased mortality associated with cessation of buprenorphine[30]

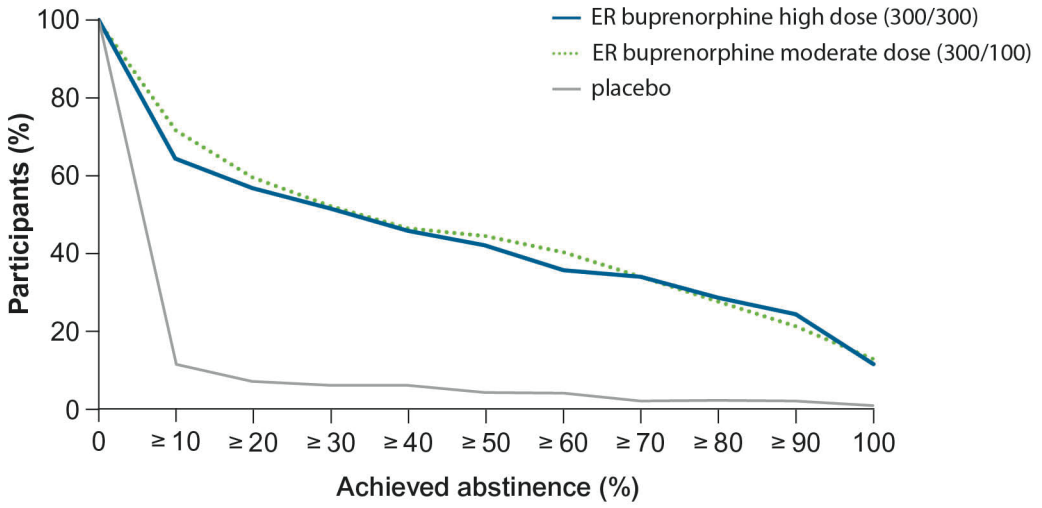


The efficacy of buprenorphine was also demonstrated in a 2015 trial that randomized 329 emergency department patients with OUD to one of three interventions: standard referral for treatment; brief intervention that included facilitated referral to community-based treatment; or brief intervention and buprenorphine initiation.[49] 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%).[50]

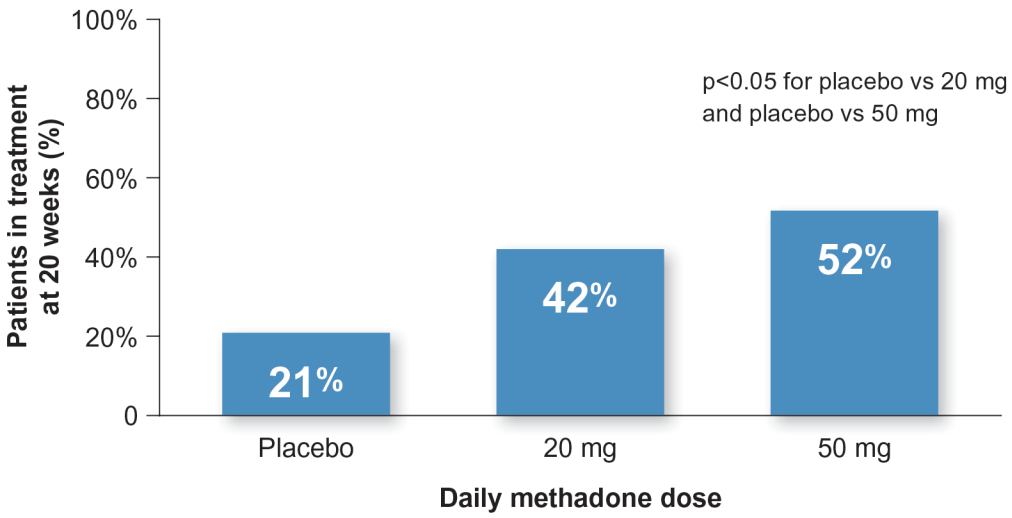
Figure 6: Extended-release buprenorphine is also effective at preventing return to opioid use [50]



Methadone

Across all populations, methadone is associated with higher retention rates than placebo. One trial randomized 247 patients to three groups: counseling alone, counseling plus methadone 20 mg/day, or counseling plus methadone 50 mg/day.[51] Both methadone doses were more effective than counseling alone at 20 weeks ($P<0.05$ for both comparisons).

Figure 7: Methadone significantly improved treatment retention at 20 weeks[51]

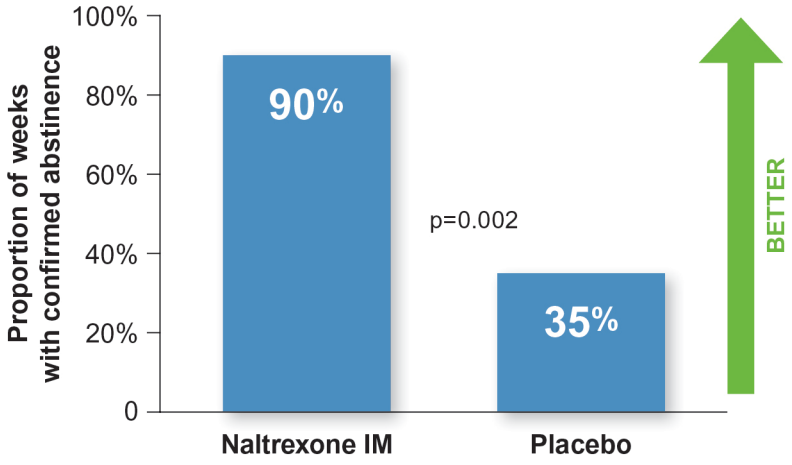


A trial comparing methadone maintenance therapy plus psychosocial therapy vs. a detoxification regimen that included psychosocial therapy, education sessions, and group therapy found significantly higher lengths of treatment retention with methadone maintenance therapy (median 438.5 days vs. 174 days, P<0.001).[52] 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.[9,53] 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.[54] At 24-week follow-up, 90% in the naltrexone group were abstinent compared to 35% in the placebo group (P=0.002).

Figure 8: Improved abstinence with naltrexone vs. placebo[54]



The 2018 open-label X:BOT trial randomized 570 adults with OUD to monthly ER naltrexone vs. daily self-administered buprenorphine/naloxone sublingual film.[53] 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 preferred options for treating OUD.

Comparative effectiveness of OUD medications

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).[55]

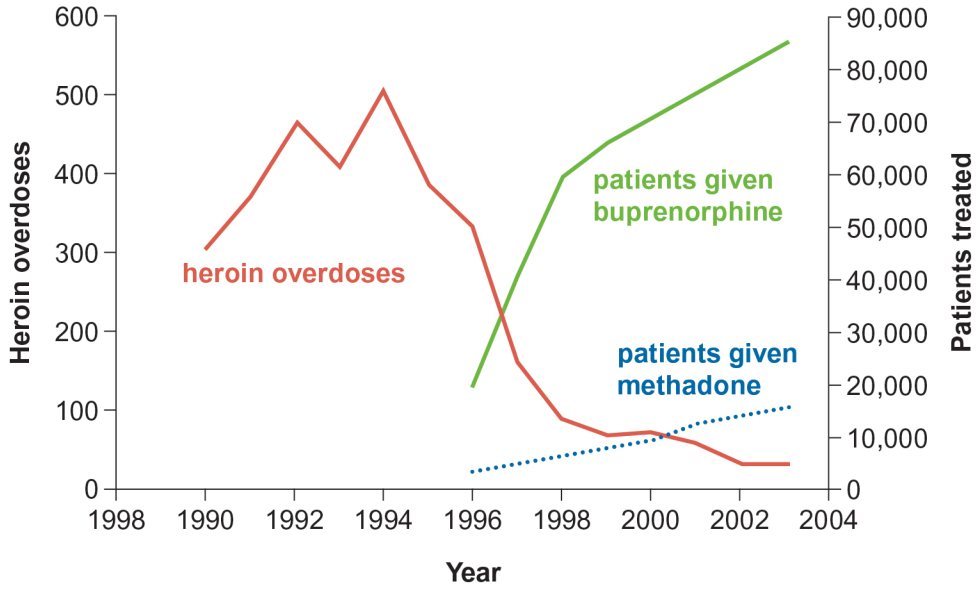
A 2014 Cochrane review of 31 trials involving 5,430 opioid-dependent persons (including dependence on both prescription and illicit opioids) found that buprenorphine administered in flexible doses adjusted to patient needs was slightly less effective than methadone for retaining participants in treatment (RR 0.83; 95% CI: 0.72-0.95).[47] 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).[56] 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

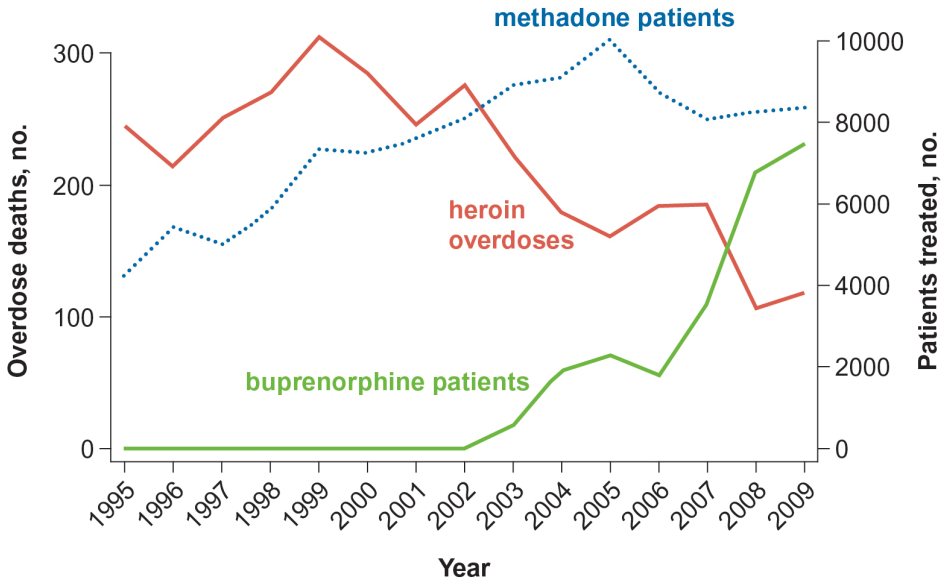
Compelling evidence for the efficacy of medication-based treatment also comes from population-level studies. Facing rising levels of heroin overdoses in the 1990s, France, in 1996, increased the availability of methadone and buprenorphine by allowing primary care physicians to prescribe both medications without getting additional certifications (both medications were also subsidized by the government).[57] As illustrated in Figure 9, heroin deaths declined rapidly as use of medication treatment increased.

Figure 9: Impact on heroin overdoses with rising use of methadone and buprenorphine[57]



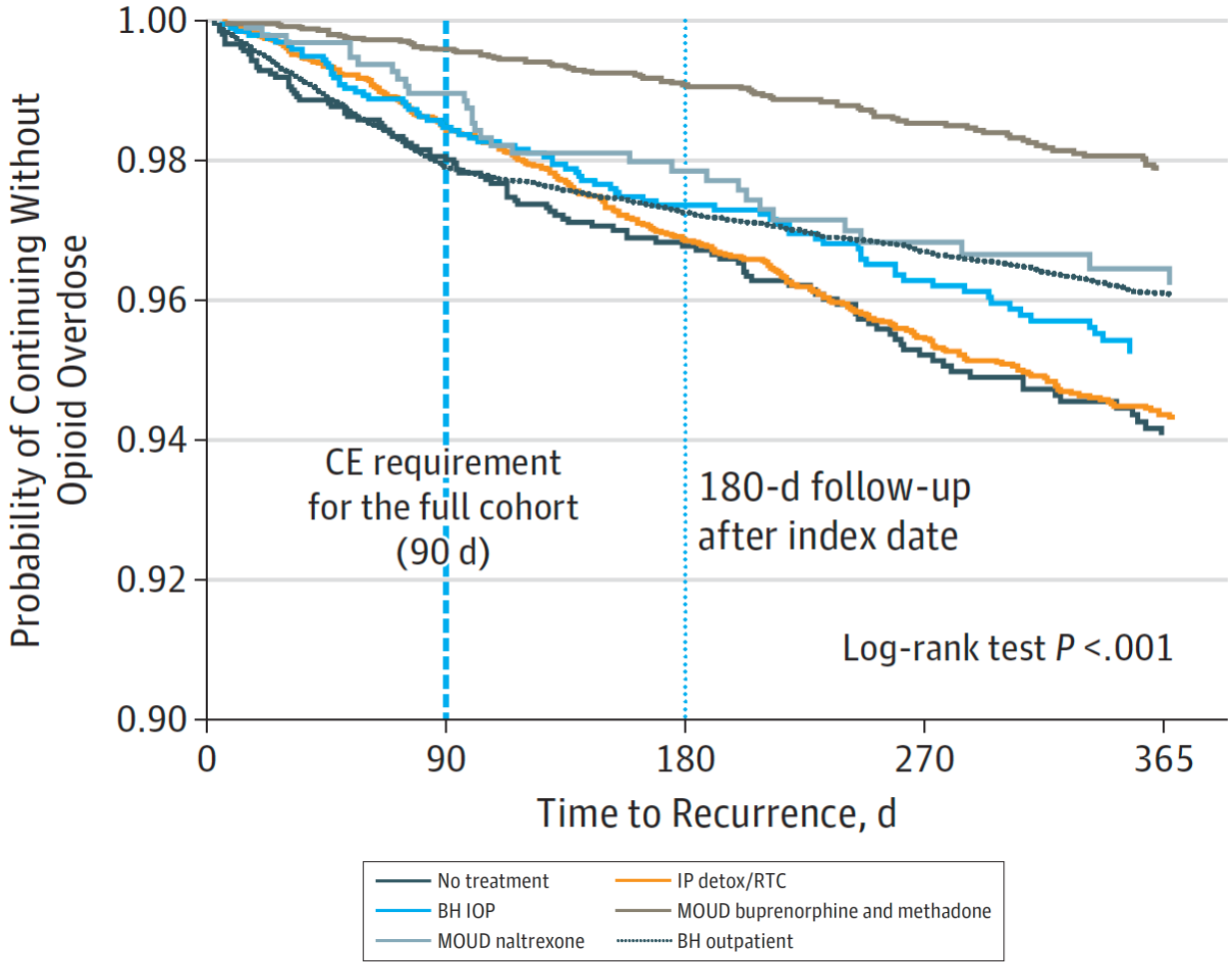
A similar pattern was observed in Baltimore, where overdose deaths declined as use of buprenorphine increased (Figure 10).[58]

Figure 10: Comparison of relapse rates in Baltimore with different OUD treatments[58]



In terms of comparing different treatments for OUD, a 2020 retrospective comparative efficacy study compared opioid-related overdose or serious acute care use, defined as 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 and methadone treatment alone were associated with reduced risk for overdose and acute care use.[24]

Figure 11: Only patients who receive buprenorphine or methadone for OUD are less likely to experience an opioid overdose[24]



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 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:[23]

- 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 (OEND)
- education and safety planning for those with a history of suicidal ideation or attempt[59]
- 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

In 2020, the FDA issued a change in labeling recommending all health care professionals prescribing opioid pain medications and medications to treat OUD discuss naloxone with patients.[60]

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 ("detox") 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.[61] 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.

Practical advice for selecting a medication for OUD

As described in the section summarizing evidence of efficacy, buprenorphine, methadone and ER naltrexone all have evidence of efficacy in the treatment of OUD. 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 for 7-10 days 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 on the following page. Although medication to treat OUD is often provided along with behavioral or cognitive-behavioral therapy, medications are effective with or without psychosocial treatment.[62] 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

	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	anyone with a DEA X-waiver**	federally-regulated opioid treatment program	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	requires daily clinic visits for supervised administration	monthly injection
Patient characteristics	**buprenorphine is preferred for most patients**	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

*Buprenorphine is often combined with naloxone (e.g., Suboxone) to prevent misuse if injected; naloxone in sublingual formulations has little to no effect if taken as prescribed.
**Since April 2021, an X-waiver can be obtained by filling out a simple form on the SAMHSA website. There is no longer a training requirement if treating fewer than 30 patients.

Clinicians without an X-waiver can still support the patient's path to recovery by taking the following steps:[23]

- assessing and treating comorbid conditions
- using motivational interviewing techniques to promote safer behaviors and encourage participation in medication treatment for OUD with other providers (SAMHSA provides an online service for finding local buprenorphine practitioners at: samhsa.gov/medication-assisted-treatment/practitioner-program-data/treatment-practitioner-locator)
- educating the patient about ways to reduce overdose risk
- discussing harm reduction strategies around safer drug use and reducing infectious complications

- prescribing naloxone to the patient and/or family members
- informing patients who inject drugs about ways to access sterile injecting equipment (including prescribing sterile syringes)
- scheduling follow-up visits regardless of referral status
- submit a Notice of Intent for an application to receive an X-waiver, which no longer requires special training if treating 30 or fewer patients (buprenorphine.samhsa.gov/forms/select-practitioner-type.php).

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.[9,36] Psychosocial treatment includes, at a minimum:[36]

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

Among evidence-based psychosocial treatments, the most effective option for OUD is contingency management (CM), which provides immediate positive reinforcers for aspects of treatment engagement and progress; unfortunately, CM is not available in most U.S. patient care settings.[63]

Peer support groups such as Narcotics Anonymous (NA), Alcoholics Anonymous (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.

Psychosocial and/or behavioral interventions can help treat the “whole patient” (e.g., comorbid psychiatric symptoms, social support needs). In recent years, mindfulness-based interventions have garnered attention for their efficacy in patients with overlapping opioid misuse and chronic pain.[64] These behavioral interventions, however, may not be available to all patients or may be under-used.[9]

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.[9] 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.[65] 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.[66-68]

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.[9,69]

Drug testing

In the context of OUD, drug 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.[70] When the right test is selected for the right person at the right time, drug tests can help clinicians:[70]

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

Drug 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 drug testing in the management of OUD is currently based primarily on expert consensus as articulated in various guidelines.[36,70,71]

Drug 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:[70]

- 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 drug testing has the most evidence supporting it, sometimes urine drug 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 physicians who are experts in addiction and pain were only able to correctly interpret three out of seven urine drug screen results.[72] Prior to ordering drug testing, the healthcare professional should ask the patient when the last dose of the prescribed opioid (or buprenorphine) was taken.

A positive drug 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 drug screen.[73] A positive drug test does *not*:[70]

- 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:[70]

- 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 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[23]

It is important not to over-interpret a negative drug 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 drug 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 drug screening in health outcomes of people with OUD. Evidence suggests that urine drug screening frequency reflects philosophy rather than clinical needs or outcomes.[74] Therefore, cautious interpretation and utilization of urine drug screening should be utilized when treating patients with OUD. As evidence of their limited utility, during the Covid-19 pandemic, the transition to telemedicine and disruption of routine frequency drug testing for patients with OUD has not translated to poorer patient outcomes.[75,76] Use of drug 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.[9] 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.[77]

Nonetheless, some patients who have stable OUD managed with opioid agonist therapy may wish to stop 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 short (7 day) vs 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.[78] 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 (if waivered), referring to treatment (if not waivered), 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. Intranasal naloxone saves lives and should be prescribed to patients with OUD and others at high risk for experiencing or responding to an opioid overdose.

Buprenorphine prescribing in primary care

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).

Traditionally, patients took their first dose of buprenorphine in an observed office setting, which was time and resource intensive. However, data now shows that it is just as safe and effective for patients to start buprenorphine at home. One study of 115 patients found no difference in treatment retention at 30 days (78.1% office vs. 78.4% home, OR 0.98; 95% CI: 0.35-2.70). Patients described difficulties with induction with similar frequencies between the office (17%) and at home inductions (17%).[79] Another study of 108 patients starting buprenorphine at home found treatment retention was 73% at seven days without any cases of precipitated withdrawal.[80] A third study identified 228 patients who had been initiated on buprenorphine at home by two primary care clinicians; only one patient developed severe precipitated withdrawal.[81]

While home inductions are often easier for patients and clinicians, some patients are not ideal candidates for home inductions. Characteristics that suggest that starting buprenorphine in office may be preferred:

- recent benzodiazepine use
- insufficient self-management skills
- low health literacy
- inability to follow up with clinic throughout initiation

While buprenorphine can also be initiated in an office or an Opioid Treatment Program, here we will focus on home-initiations as this is now the most common setting in the primary care setting.[80,81]

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.

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.

Precipitated withdrawal can be avoided by either:

- **Standard initiation** (recommended for most primary care settings): 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 initiation** (recommended for patients at high risk for precipitated withdrawal, with assistance of specialist): 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. This approach has become increasingly applied as patients present with illicitly manufactured fentanyl use.

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.

Table 3: 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).[82] 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.[83]

Measuring opioid withdrawal

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 Clinical Opiate Withdrawal Scale (COWS) to assess withdrawal severity.[84] A link to a printable version of this tool can be found at drugabuse.gov/sites/default/files/files/ClinicalOpiateWithdrawalScale.pdf

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. Specifically, clinicians should review the following:

- Buprenorphine is an opioid, so if discontinued 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 and left for 10-15 minutes to dissolve. 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.
- 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).

Initiating 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. Notably as detailed above patients using long-acting opioids such as methadone or fentanyl will need to wait at least 48 to 72 hours before starting buprenorphine or pursue a low-dose buprenorphine initiation with the guidance of a specialist.

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).[85]

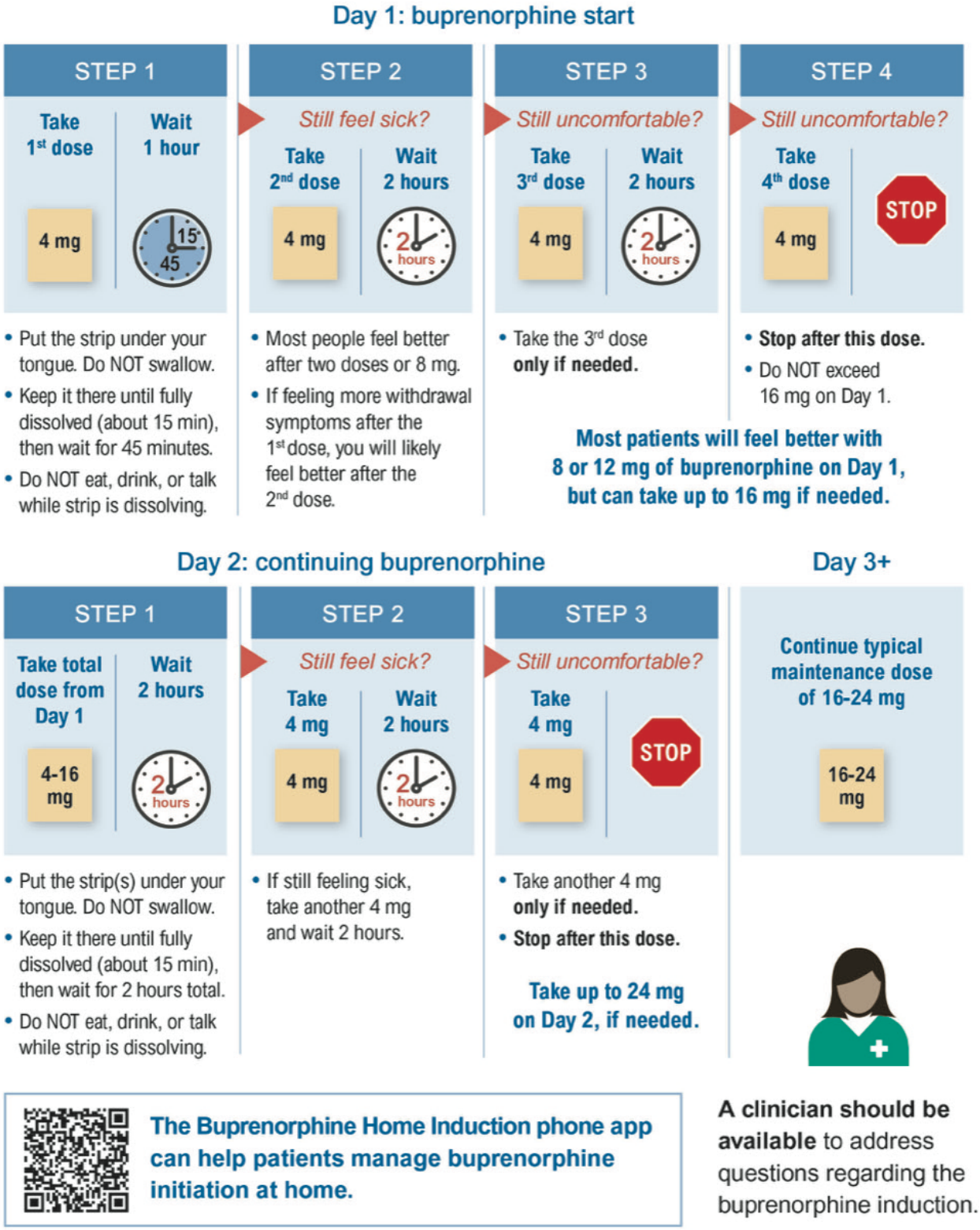
Practically, for initiation, clinicians can prescribe enough buprenorphine for 1 week at the anticipated dose (often buprenorphine-naloxone (Suboxone) 8-2 mg twice daily. Clinicians should provide instructions for patients (an example in Figure 12 on the next page) and can prescribe the following comfort medications to ease withdrawal symptoms:

- 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

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.

Figure 12: Patient instructions for buprenorphine home initiation



Maintenance

Maintenance occurs when a patient is doing well on a steady dose of buprenorphine. The common daily dose is 16 to 24 mg of buprenorphine.[85] Increasing the dose to 32 mg may be an option used by some specialists based on patient characteristics. The length the maintenance phase is tailored to each patient and could be indefinite due to the high risk of relapse (see section on Treatment duration on page 21).

Misconceptions about OUD treatment

Stigma and misunderstanding surround addiction generally and OUD in particular.[9] 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 medication treatment has evolved in the past 15 years.[86] Table 4 (next page) summarizes some common misconceptions about OUD and the corresponding realities.

Table 4: OUD treatment: Misconceptions vs. realities[8]

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 many 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, 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.[9] 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.[87] 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).[88] 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,[89] which erodes their psychological well-being and may deter them from seeking treatment.[9]

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.[90]

Table 5: Alternatives to stigma-reinforcing words and phrases[90]

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

Here are some tips for creating an inclusive, non-stigmatizing medical practice:[23]

- 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 responsibility.
- 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.

Obtaining an X-waiver

> *"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 and waivered primary care physician in the Boston area

Due to historic regulations dating back to the Harrison Narcotic Act of 1914, prescribers have been prevented from prescribing of opioids for patients with OUD. As a result, clinicians in the U.S. must obtain a waiver from the Drug Enforcement Administration to prescribe buprenorphine. This waiver is informally called an "X-waiver" because waivered practitioners have an "X" added before their DEA registration number.

Currently, obtaining an X-waiver takes 5 minutes and can be completed by submitting a "Notice of Intent" on SAHMSA's website (buprenorphine.samhsa.gov/forms/select-practitioner-type.php). Previously, physicians had to complete an 8-hour training course, but this requirement was revoked in 2021 so that the training is only required if a practitioner plans to prescribe buprenorphine for more than 30 patients concurrently. An X-waiver is only required when prescribing buprenorphine to treat OUD; use of buprenorphine to chronic pain does not require an X-waiver.

Since 2016, a range of non-physician clinicians have also become eligible to obtain X-waivers, including nurse practitioners, physician assistants, certified nurse midwives, certified nurse anesthetists, and certified nurse specialists. The training requirement is waived for these clinicians when prescribing to fewer than 30 patients. Twenty-four hours of training is required if prescribing for more.[86] Only clinicians authorized by their states to prescribe Schedule III medications may prescribe buprenorphine.

Clinicians with X-waivers are allowed to treat up to 30 patients in the year after obtaining their waiver, 100 patients in the following year, and 275 patients annually thereafter, with each increase in waiver capacity having to be applied for and authorized. Some physicians meeting additional criteria (i.e., board certified in addiction medicine or practicing in a qualified practice setting), can begin with a 100-patient limit immediately after getting their waiver.[91] Clinicians with X-waivers have the option to be listed on SAMHSA's physician and treatment locator site samhsa.gov/medication-assisted-treatment/physician-program-data/treatment-physician-locator.

Both the 8-hour and 24-hour waiver courses are available from some professional societies, or are available free from the Providers' Clinical Support System (PCSS), which is a coalition of healthcare organizations led by the American Academy of Addiction Psychiatry to train primary care and other healthcare professionals to treat patients with OUD (available at: pcssnow.org/education-training/). PCSS provides extensive clinical support tools, on-demand webinars, discussion roundtables, and experienced clinical mentorship all free of charge.

Despite strong recommendations from SAMHSA that more physicians, NPs, and PAs obtain X-waivers,[92] and advocacy efforts to eliminate the waiver process entirely,[93] only an estimated 3% of physicians have such waivers.[94] Of the clinicians who are waivered, many do not prescribe to their capacity. According to one estimate, fewer than 30% of physicians with X-waivers actually prescribe buprenorphine, and less than half are listed on the SAMHSA locator site.[95] The median number of monthly patients that a waivered clinician prescribed was only 8.[96]

BOTTOM LINE: Despite an urgent need, many clinicians have not obtained DEA X-waivers. Becoming X-waivered can broaden access to life-saving and life-enhancing buprenorphine for the treatment of OUD, and can be clinically 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.

Preventing overdose

Naloxone prescription and education

Naloxone (e.g., Narcan), an opioid antagonist, immediately reverses the effects of opioids. It should be prescribed to any patient who is prescribed or uses opioids, particularly those taking >50 morphine milligram equivalents per day, 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.[97] 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.[98]

Medications for OUD

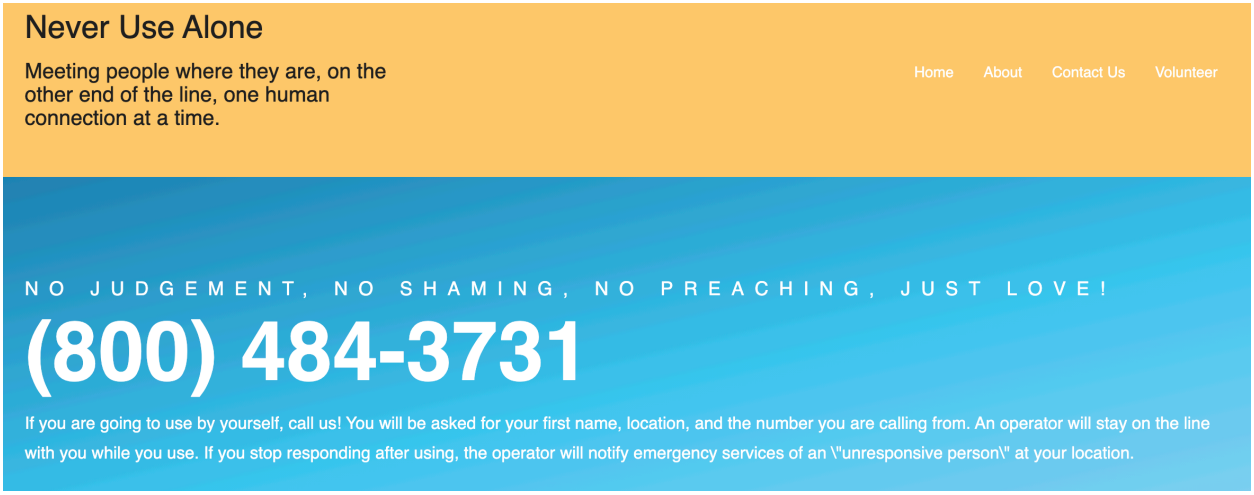
As described previously, medications for OUD (particularly buprenorphine and methadone) are extremely effective in preventing opioid overdose. Importantly, these medications prevent overdose even if patients continue to use additional opioids. Therefore, medications for OUD should never be discontinued 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. With this knowledge, they can take steps such as ensuring they do not use alone or taking a test dose, to prevent overdose.

Preventing use alone

Clinicians can offer patients resources for bystanders in case the patient does have an unintentional overdose. There is a “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 (smoking) drug use are associated with increased risk for bacterial and viral infections. Certain use practices such as sharing injection or smoking supplies places 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 bacteremia or 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 these viral infections at least annually, and more frequently if they have frequent 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.[99] Information regarding syringe exchange program locations can be found at nasen.org. Notably if there is no local syringe exchange program, 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 generics, Descovy); there is also a long-acting injection (Apretude). PrEP is indicated for

people who inject drugs who 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.[100] 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 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).[101] In addition to other methods of pain management, it can therefore be helpful to also 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 any 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.[23] Those who attempt to overcome the opioid blockade with high doses of opioids are at high risk for overdose.[102]

If opioids are deemed necessary for patients on methadone or buprenorphine, clinicians should verify the patient's methadone or buprenorphine dose, and ensure that naloxone is available in the event of suspected overdose. Clinicians should inform the program or prescribing physician about the addition of new opioids (or any other controlled substance), as this may affect subsequent urine drug 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.[103]

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.[104] 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).[105] 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.[106]

Both methadone and buprenorphine are recommended for treating OUD in pregnancy to improve outcomes for both mother and newborn.[9] 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.[107]

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.[108] Other outcomes and adverse events were similar between the two groups. Although it is common to 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.[109]

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.[9] Naloxone in life-threatening emergencies is recommended.

Despite data supporting medication use, most pregnant women with OUD do not receive any treatment.[110] 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.[9]

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.

Recovery

As with other chronic diseases such as asthma or diabetes, the goal of treatment for OUD not a "cure." But 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.[111]

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.[111] Relapse rates for drug use are similar to rates of relapse for patients treated for hypertension or asthma.[112] 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:[113]

- 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.

BOTTOM LINE: OUD can be managed successfully. Return to opioid use is 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

More than 2.7 million people in the United States 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.[8,9] 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. However, most people with OUD in the United States receive no treatment, and not enough clinicians have obtained the X-waivers needed to meet the treatment gap.

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 naloxone, and ensure it is available to all patients with OUD and those who are at risk for experiencing or responding to an opioid overdose—it can be lifesaving.
- All licensed physicians, NPs, and PAs can now obtain an X-waiver by submitting a “Notice of Intent” (only a 5-minute process) without undergoing a training to prescribe buprenorphine to less than 30 patients concurrently for OUD.
- 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 7.18.22

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About this publication

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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