Opioid Use Disorder: Pharmacotherapy Part 2

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Part 3 Contents

Chapter 3D: Buprenorphine

Chapter 3D is an overview of buprenorphine pharmacology and specific dosing guidance for sublingual and buccal formulations and buprenorphine implants.

Buprenorphine and buprenorphine/naloxone formulations are effective treatments for opioid use disorder (OUD). Numerous clinical studies and randomized clinical trials have demonstrated buprenorphine's efficacy in retaining patients in treatment and reducing illicit opioid use compared with treatment without medication and medically supervised withdrawal.[211,212,213] Other research has associated it with reduction in HIV risk behavior and risk of overdose death, and its effectiveness has been shown in primary care settings.[214,215,216,217,218] Buprenorphine is on the World Health Organization (WHO) list of essential medications.[219]

The Treatment Improvement Protocol (TIP) expert panel recommends offering the option of Food and Drug Administration (FDA)-approved buprenorphine formulations to appropriate patients with OUD, considering patient preferences for and experience with other medications or no medication. These recommendations align with recent Department of Veterans Affairs guidelines.[220]

Formulations

History of Approvals

Opioid treatment programs (OTPs) may administer or dispense buprenorphine but only providers with Substance Abuse and Mental Health Services Administration (SAMHSA) waivers can prescribe buprenorphine for OUD. See "Resource Alert: How To Obtain a Waiver To Prescribe Buprenorphine" in Chapter 3A of this TIP.

FDA originally approved buprenorphine for analgesia. Formulations for OUD treatment were approved in:

- 2002: Sublingual buprenorphine/naloxone sublingual tablets (Suboxone); buprenorphine sublingual tablets (Subutex). The manufacturer discontinued the tablet dosage of the latter from the U.S. market after the film's approval, but generic tablet formulations are still available (Exhibit 3A.4, Chapter 3A).
- 2010: Buprenorphine/naloxone sublingual films.
- 2013: Buprenorphine/naloxone sublingual tablets (Zubsolv).[221]
- 2014: Buprenorphine/naloxone buccal films (Bunavail).[222]
- 2016: Buprenorphine implants (Probuphine).
- 2017: Buprenorphine extended-release injection (Sublocade).

FDA approved generic buprenorphine and buprenorphine/naloxone formulations based on evidence that they produce similar (within 90 percent confidence intervals) bioequivalence on pharmacokinetic measures, such as peak serum concentration, compared with the original sublingual buprenorphine/naloxone product.

The 2013 and 2014 branded formulations have greater bioavailability than Suboxone, meaning they deliver more buprenorphine to the bloodstream, thus achieving the same effect as the original product with lower doses. For example, 5.7 mg/1.4 mg of Zubsolv and 4.2 mg/0.7 mg of Bunavail provide the same buprenorphine exposure as 8 mg/2 mg of Suboxone.

Exhibit 3D.1 lists product strengths and recommended once-daily maintenance doses. For simplicity, dosing information here refers to sublingual Suboxone equivalents. An 8 mg/2 mg tablet of sublingual Suboxone is equivalent to 5.7 mg/1.4 mg of sublingual Zubsolv and 4.2 mg/0.7 mg of buccal Bunavail.

Patients who switch formulations may experience clinically significant plasma concentration changes that may require dose adjustments; bioavailability is similar, but not identical, between formulations.

Exhibit 3D.1 Buprenorphine Transmucosal Products for OUD Treatment

Product Name/Active Ingredient	Route of Administration/Form	Available Strengths	Recommended Once-Daily Maintenance Dose
Bunavail[223] • Buprenorphine hydrochloride • Naloxone hydrochloride	Buccal film	2.1 mg/0.3 mg 4.2 mg/0.7 mg 6.3 mg/1 mg	Target: 8.4 mg/1.4 mg Range: 2.1 mg/0.3 mg to 12.6 mg/2.1 mg
Generic combination product[224,225] • Buprenorphine hydrochloride • Naloxone hydrochloride	Sublingual tablet	2 mg/0.5 mg 8 mg/2 mg	Target: 16 mg/4 mg Range: 4 mg/1 mg to 24 mg/6 mg*
Generic monoproduct[226,227] • Buprenorphine hydrochloride	Sublingual tablet	2 mg 8 mg	Target: 16 mg Range: 4 mg to 24 mg*
Suboxone[228,229] • Buprenorphine hydrochloride • Naloxone hydrochloride	Sublingual film	2 mg/0.5 mg 4 mg/1 mg 8 mg/2 mg 12 mg/3 mg	Target: 16 mg/4 mg Range: 4 mg/1 mg to 24 mg/6 mg*
Zubsolv[230,231] • Buprenorphine hydrochloride • Naloxone hydrochloride	Sublingual tablet	0.7 mg/0.18 mg 1.4 mg/0.36 mg 2.9 mg/0.71 mg 5.7 mg/1.4 mg 8.6 mg/2.1 mg 11.4 mg/2.9 mg	Target: 11.4 mg/2.9 mg Range: 2.9 mg/0.71 mg to 17.2 mg/4.2 mg

* Dosages above 24 mg buprenorphine or 24 mg/6 mg buprenorphine/naloxone per day have shown no clinical advantage.[232,233]

Adapted from material in the public domain.[234]

Implants

In 2016, FDA approved buprenorphine implants for OUD maintenance treatment in patients who have achieved sustained clinical stability (e.g., periods of abstinence, minimal or no desire to use illicit opioids, stable housing, social support) while taking no more than 8 mg of daily Subutex (buprenorphine monoproduct) or Suboxone (buprenorphine/naloxone) equivalents. The implants are a set of four rods, each 2.5 mm in diameter and 26 mm in length. Each rod contains the equivalent of 80 mg of buprenorphine hydrochloride. The implants are for subdermal insertion on the inside of the upper arm and provide 6 months of buprenorphine. The implants must be removed after 6 months.

Peak buprenorphine plasma concentrations occur 12 hours after implant insertion, slowly decrease, and reach steady-state concentrations in about 4 weeks. Steady-state concentrations are comparable to trough buprenorphine plasma levels produced by daily sublingual buprenorphine doses of 8 mg or less. Implant effectiveness lasts up to 6 months.

Injectables

In November 2017, FDA approved extended-release (monthly) subcutaneous injectable buprenorphine for moderate-to-severe OUD treatment among patients who initiated treatment with transmucosal buprenorphine, followed by at least 7 days of dose adjustment. It is available in two doses, 300 mg/1.5 mL and 100 mg/0.5 mL. Both are stored refrigerated in prefilled syringes with safety needles and administered by subcutaneous injection in the abdomen. The first two monthly doses recommended are 300 mg each followed by a 100 mg monthly maintenance dose. Peak buprenorphine concentrations occur about 24 hours after the injection. Steady state is achieved after 4 to 6 months. After discontinuation, patients may have detectable plasma levels of buprenorphine for 12 months or longer. Duration of detection in urine is not known.[235]

Pharmacology

Buprenorphine, an opioid receptor partial agonist, is a schedule III controlled medication derived from the opium alkaloid thebaine. Through cross-tolerance and mu-opioid receptor occupancy, **at adequate doses, buprenorphine reduces opioid withdrawal and craving and blunts the effects of illicit opioids.**

Buprenorphine binds tightly to the mu-opioid receptor because of its particularly high receptor affinity. This prevents other opioids with lower affinity (e.g., heroin) from binding. The net result is a blunting or blocking of the euphoria, respiratory depression, and other effects of these opioids.

Buprenorphine has less potential to cause respiratory depression, given its ceiling effect. As a partial agonist, buprenorphine's maximum effect on respiratory depression is more limited than full agonists. Once reaching a moderate dose, its effects no longer increase if the dose is increased.[236,237,238]

There is wide individual variability in buprenorphine pharmacokinetics. For example, the mean time to maximum plasma buprenorphine concentration after a single sublingual dose ranges from 40 minutes to 3.5 hours.[239] Thus, after providing the first dose of buprenorphine, wait at least 2 hours to decide whether a second dose is necessary.

Buprenorphine has a long elimination half-life, which varies from 24 to 69 hours[240] with a mean half-life of 24 to 42 hours.[241] It dissociates slowly from the receptor.

Buprenorphine can be safely dosed (even at double the *stabilized* dose) less than daily.[242] For example, a patient *stabilized* on 12 mg of buprenorphine/naloxone daily can be treated with 24 mg every other day or 24 mg on Monday/Wednesday and 36 mg on Friday. Such schedules reduce travel burden for patients who need or want supervised dosing at an OTP or a clinic. Such schedules may also be useful for patients who must spend weekends in jails that disallow buprenorphine dosing.

Bioavailability

Buprenorphine has poor oral compared with sublingual and buccal bioavailability. Naloxone, a short-acting mu-opioid receptor antagonist, has very poor oral, sublingual, and buccal bioavailability but is absorbed when injected or snorted. The addition of naloxone decreases buprenorphine's potential for misuse. In the Suboxone formulation of buprenorphine/naloxone, the ratio of buprenorphine to naloxone is 4:1. The ratio of buprenorphine to naloxone varies across products, as the absorption of both active ingredients is different for buccal versus sublingual films versus tablets.

Buprenorphine/naloxone transmucosal products are abuse-deterrent formulations, although they can still be misused. When a patient takes these formulations as prescribed, he or she absorbs buprenorphine but only a biologically negligible amount of naloxone. But if crushed or dissolved for intranasal or intravenous (IV) misuse, both medications are bioavailable. Naloxone then blunts the immediate opioid agonist effects of buprenorphine. It also induces opioid withdrawal in people who are physically dependent on opioids. This reduces misuse liability compared with transmucosal formulations with buprenorphine alone.[243,244]

Subdermal buprenorphine implants release buprenorphine in steady concentrations over 6 months. These concentrations are approximately equivalent to 8 mg or less of the buprenorphine sublingual formulations. Once implanted, these rods are unlikely to be diverted.

Extended-release buprenorphine for subcutaneous injection releases buprenorphine over at least a 1-month period. After injection, an initial buprenorphine plasma level peaks around 24 hours and then slowly declines to a plateau. With monthly injections, steady state is reached at 4 to 6 months.[245]

Metabolism and Excretion

Buprenorphine:[246,247]

- Is highly plasma bound.
- Crosses the blood–brain barrier readily because of its high lipid solubility.
- Is excreted in urine and feces.
- Has only one known pharmacologically active metabolite: norbuprenorphine.

Be aware of potential CYP450 3A4 inducers,[248] substrates, and inhibitors while monitoring for potential drug–drug interactions (see the "Drug Interactions" section below). Buprenorphine undergoes metabolism in the liver primarily by cytochrome P450 (CYP450) 3A4 enzymes. Coadministration of other medications metabolized along this pathway can affect the rate of buprenorphine metabolism.

Buprenorphine has fewer clinically relevant drug interactions than methadone in general. For detailed explanations of metabolism and excretion, see the package inserts for each buprenorphine product.

Dosing Considerations

Buprenorphine is used for the treatment of OUD. Formulations are available as sublingual tablets and film, buccal film, implants, and extended-release injection (Exhibit 3A.4 in Chapter 3A of this TIP).

Contraindications

Buprenorphine is contraindicated in patients who are allergic to it. Patients with true allergic reactions to naloxone should not be treated with the combination buprenorphine/naloxone product. Allergy to naloxone is infrequent. Some patients may falsely or mistakenly claim an allergy to naloxone and request buprenorphine monoproduct. Carefully assess such claims and explain the differences between an allergic reaction and symptoms of opioid withdrawal precipitated by buprenorphine or naloxone; the monoproduct has more abuse liability than buprenorphine/naloxone.[249]

Precautions and Warnings

- **Respiratory depression and overdoses are uncommon in adults, but they do happen.**[250] Most fatal overdoses involve IV buprenorphine misuse or concurrent central nervous system depressant

use, including high doses of benzodiazepines, alcohol, or other sedatives.[251,252] However, fatal overdoses have been reported in opioid-naïve patients treated with 2 mg buprenorphine for pain.[253] Exhibit 3D.2 summarizes the management of patients with preexisting respiratory impairment.

- **Unintentional pediatric exposure can be life threatening or fatal.**[254] Thus, emphasize safe storage of medication, and teach patients to remove any buprenorphine found in a child's mouth immediately (even if it was only a partial tablet or film). Call 9-1-1 so the child can go to the nearest emergency department for immediate medical attention.
- **Cases of hepatitis and liver failure exist but often involve predisposing hepatic risk factors,** such as preexisting liver enzyme abnormalities, hepatitis B or C infections, and use of other potentially hepatotoxic drugs or IV drugs. A multisite randomized trial of hepatic effects in patients taking methadone or buprenorphine found no evidence of liver damage in the first 6 months of treatment. The authors concluded that prescribing these medications should not cause major concern for liver injury.[255] Exhibit 3D.2 summarizes management of patients with hepatic impairment.
- **Potential for misuse and diversion exists.** People can misuse buprenorphine via intranasal or IV routes or divert it for others to misuse. Do not give early or multiple refills without careful assessment and monitoring suited to the patient's level of stability.[256,257]

Exhibit 3D.2. Medication Management for Patients With Respiratory or Hepatic Impairment

Contraindication/Caution	Management
Compromised Respiratory Function (e.g., chronic obstructive pulmonary disease, decreased respiratory reserve, hypoxia, hypercapnia [abnormally elevated blood levels of carbon dioxide], preexisting respiratory depression).	• Prescribe with caution; monitor closely. • Warn patients about the risk of using benzodiazepines or other depressants while taking buprenorphine.[258] • Support patients in their attempts to discontinue tobacco use.
Hepatic Impairment: Buprenorphine and naloxone are extensively metabolized by the liver. Moderate-to-severe impairment results in decreased clearance, increased overall exposure to both medications, and higher risk of buprenorphine toxicity and precipitated withdrawal from naloxone. These effects have not been observed in patients with mild hepatic impairment.[259,260]	• Mild impairment (Child-Pugh score of 5–6):[261] No dose adjustment needed. • Moderate impairment (Child-Pugh score of 7–9):[262] Combination products are not recommended; they may precipitate withdrawal. *Use combination products cautiously for maintenance treatment in patients who've been inducted with a monoproduct;[263,264] monitor for signs and symptoms of buprenorphine toxicity or overdose.[265] Naloxone may interfere with buprenorphine's efficacy.[266,267] • Severe impairment (Child-Pugh score of 10–15):[268] Do not use the combination product.[269] For monoproduct, consider halving the starting and titration doses used in patients with normal liver function; monitor for signs and symptoms of toxicity or overdose caused by increased buprenorphine levels.[270]
*Moderate-to-severe impairment results in much more reduced clearance of naloxone than of buprenorphine. Nasser et al.[271] found that moderate impairment doubled or tripled exposure (compared with subjects with no or mild impairment) for both medications. In subjects with severe impairment, buprenorphine exposure was also two to three times higher; naloxone exposure increased more than tenfold. *Adapted from material in the public domain.*[272]	

Discourage misuse and diversion by:

- Requiring frequent office visits until patients are stable.
- Testing urine for buprenorphine and norbuprenorphine or buprenorphine glucuronide (both metabolites of buprenorphine).
- Using other methods to ensure adequate adherence to the medication as prescribed, such as developing and adopting a diversion control plan (see Chapter 3E: Medical Management Strategies).

- **Adrenal insufficiency has been reported** with opioid use, most often after more than 1 month of buprenorphine maintenance.[273]
- **Patients will develop physical dependence on buprenorphine.** Alert patients that they'll experience opioid withdrawal if they stop buprenorphine.
- **Buprenorphine may affect cognition and psychomotor performance and can have sedating effects** in some people (particularly those who've lost tolerance after a period of abstinence from opioids). Concurrent use of illicit drugs, other prescribed medications, or medical or psychiatric comorbidity can affect cognition and psychomotor performance. Urge patients to exercise caution in using heavy machinery and driving until they're sure that their abilities are not compromised.[274]
- **Allergic reactions** have occurred in patients treated with buprenorphine, including rash, urticaria, angioedema, and anaphylaxis.
- **Buprenorphine can cause precipitated opioid withdrawal.** It has weaker opioid agonist effects and stronger receptor affinity than full agonists (e.g., heroin, methadone). It can displace full agonists from receptors, precipitating opioid withdrawal.[275] Factors affecting this possibility include:
  - Current level of opioid physical dependence. The higher the level of physical dependence, the higher the likelihood of precipitating withdrawal.[276] Ensuring that patients are in opioid withdrawal when initiating buprenorphine decreases this risk.
  - Time since the last mu-opioid receptor full agonist dose. The longer the time since the last dose, the lower the likelihood of precipitated withdrawal.[277]
  - Dose of buprenorphine administered. The smaller the dose of buprenorphine, the less likely it is to precipitate withdrawal. [278,279]
- **Neonatal abstinence syndrome (NAS) may occur in newborns** of pregnant women who take buprenorphine. Women receiving opioid agonist therapy while pregnant should talk with their healthcare provider about NAS and how to reduce it. Not all babies born to women treated with opioid agonists require treatment for NAS. Research has shown that the dose of opioid agonist medication is not reliably related to the severity of NAS.[280,281,282] Thus, each woman should receive the dose of medication that best manages her illness.

Reducing NAS Severity

Offer the following advice to pregnant women receiving treatment with an opioid agonist:

- Avoid smoking during pregnancy.
- Avoid benzodiazepines.
- Meet with the neonatologist and/or pediatrician to learn how the hospital assesses and treats NAS and what they suggest you can do as a parent to help soothe a baby with NAS.
- Request rooming-in with the child.
- Talk with the healthcare professional providing obstetric care about breastfeeding, as this may help make NAS less severe.
- In the first week after birth, keeping lights low, speaking softly, avoiding too much stimulation, and providing frequent skin-to-skin contact can help prevent or limit symptoms of NAS.

Drug Interactions

Buprenorphine has fewer documented clinically significant drug interactions than methadone,[283] but monitoring is still needed for patients who are starting

or stopping medications that are CYP450 3A4 enzyme inhibitors or inducers for overdosing/underdosing of buprenorphine or coadministered medication. Exhibit 3D.3 lists these medications, including some anticonvulsants, antibiotics, and HIV medications (Exhibit 3D.4 lists more HIV medications). More information on drug–drug interactions is available online (www.drugs.com/drug-interactions/buprenorphine-index.html?filter=3&generic_only=).

Monitor responses to buprenorphine in patients taking nonnucleoside reverse transcriptase inhibitors. Changes in buprenorphine concentrations can be clinically significant.[284]

Combination antiretroviral therapy (atazanavir/ritonavir) increases buprenorphine and norbuprenorphine serum concentrations.[285] Case reports have demonstrated signs of buprenorphine excess (sedation). Decreasing buprenorphine can improve this symptom.[286] Other research has demonstrated no need to adjust the buprenorphine dose among patients taking atazanavir.[287]

Exhibit 3D.3. Partial List of Medications Metabolized by Cytochrome P450 3A4

Inhibitors (Potentially Increase Blood Levels of Buprenorphine)	Substrates		Inducers (Potentially Decrease Blood Levels of Buprenorphine)
Amiodarone	Alprazolam	Loratadine	Carbamazepine
Atazanavir	Amlodipine	Losartan	Dexamethasone
Atazanavir/Ritonavir	Astemizole	Lovastatin	Efavirenz
Clarithromycin	Atorvastatin	Miconazole	Ethosuximide
Delavirdine	Carbamazepine	Midazolam	Nevirapine
Erythromycin	Cisapride	Navelbine	Phenobarbital
Fluconazole	Clindamycin	Nefazodone	Phenytoin
Fluoxetine	Clonazepam	Nelfinavir	Primidone
Fluvoxamine	Cyclobenzaprine	Nicardipine	Rifampin
Grapefruit Juice	Cyclosporine	Nifedipine	
Indinavir	Dapsone	Nimodipine	
Itraconazole	Delavirdine	Ondansetron	
Ketoconazole	Dexamethasone	Oral Contraceptives	
Metronidazole	Diazepam	Paclitaxel	
Miconazole	Diltiazem	Prednisone	
Nefazodone	Disopyramide	Progestins	
Nelfinavir	Doxorubicin	Quinidine	
Nicardipine	Erythromycin	Rifampin	
Norfloxacin	Estrogens	Ritonavir	
Omeprazol	Etoposide	R-Warfarin	
Paroxetine	Felodipine	Saquinavir	
Ritonavir	Fentanyl	Sertraline	
Saquinavir	Fexofenadine	Simvastatin	
Sertraline	Glyburide	Tacrolimus	
Verapamil	Ifosfamide	Tamoxifen	
Zafirlukast	Indinavir	Verapamil	
Zileuton	Ketoconazole	Vinblastine	
	Lansoprazole	Zileuton	
	Lidocaine		

Note: Consult a point-of-service medical reference application for the most up-to-date drug–drug interactions before making medication management decisions.

Adapted from material in the public domain.[288]

For tuberculosis treatment, rifampin but not rifabutin may decrease buprenorphine concentrations. Rifampin produced opioid withdrawal in 50 percent of research volunteers with opioid dependence.[289]

Exhibit 3D.4. Potential Interactions Between Buprenorphine and HIV Medications

Medication	Type	Potential Interaction
Atazanavir	Protease inhibitor	Increased buprenorphine concentrations. May cause cognitive impairment[290,291] or oversedation.[292,293] Slower titration or dose reduction of buprenorphine may be warranted.[294,295]
Darunavir-ritonavir	Protease inhibitor	Some pharmacokinetic (PK) effect; dose adjustments unlikely to be needed, but clinical monitoring is recommended.[296]
Delavirdine	Nonnucleoside reverse transcriptase inhibitor	Increased buprenorphine concentrations, but no clinically significant effect. Dose adjustments unlikely to be needed. However, use with caution, as long-term effects (more than 7 days) are unknown.[297,298]
Efavirenz	Nonnucleoside reverse transcriptase inhibitor	Some PK effect; dose adjustments unlikely to be needed.[299]
Elvitegravir (with cobicistat)	Integrase inhibitor	Some PK effect; no dose adjustments needed.[300]
Nevirapine	Nonnucleoside reverse transcriptase inhibitor	Some PK effect; no dose adjustments needed.[301]
Ritonavir	Protease inhibitor	Some PK effect; no dose adjustments needed.[302]
Tipranavir	Protease inhibitor	Some PK effect; no dose adjustments needed.[303]

Adapted from material in the public domain.[304]

FDA warns of increased serotonin syndrome risk with prescription opioids, including buprenorphine. Serotonin syndrome can include:

- Changes in mental status.
- Fever.
- Tremor.
- Sweating.
- Dilated pupils.

Serotonin syndrome can occur with simultaneous opioid and antidepressant treatment. There are only a few case reports of serotonin syndrome with buprenorphine,[305] but be aware of this possibility given the frequent treatment of mood disorders in patients with OUD.

Side Effects

Buprenorphine's side effects may be less intense than those of full agonists. Otherwise, they resemble those of other mu-opioid agonists. Possible side effects include the following (buprenorphine FDA labels list all potential side effects https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=8a5edcf9-828c-4f97-b671-268ab13a8ecd):

- Oral hypoesthesia (oral numbness)
- Constipation
- Glossodynia (tongue pain)
- Oral mucosal erythema

- Vomiting
- Intoxication
- Disturbance in attention
- Palpitations
- Insomnia
- Opioid withdrawal syndrome
- Excessive sweating
- Blurred vision

Serious implant-related adverse events are uncommon but possible according to the FDA label (www.accessdata.fda.gov/drugsatfda_docs/label/2016/204442Orig1s000lbl.pdf). Still, more than 10 percent of patients experience implant site pain, itching, or swelling. Migration beyond the local insertion site is rare but possible, as is nerve damage. Buprenorphine may be extruded from implants for potential misuse. Insert implants only in stable patients, for whom FDA has approved this formulation.

Implants may extrude and potentially come out (e.g., from incomplete insertion or infection). Tell patients to call the implanting physician if an implant looks like it is extruding or comes out. If the implant comes out, patients should safely store and dispose of it (following local and federal regulations) to protect others from unintended exposure.

Serious injection site adverse events for the extended-release formulation are uncommon but possible. The most common injection site adverse reactions were pain (7.2 percent), pruritus (6.6 percent), and erythema (4.7 percent) in phase three trials. Two cases of surgical removal of the monthly depot were reported in premarketing clinical studies. Surgical excision under local anesthesia within 14 days of injection is possible. It is recommended that, before treatment, baseline liver function tests are assessed with monthly monitoring during treatment, particularly with the 300 mg dose. There are limited data regarding use of the extended-release injection formulation in pregnant women with OUD. In animal reproductive studies with Sublocade's excipient, N-Methyl-2-pyrrolidone, there were reported fetal adverse reactions. Women should be advised that the use of Sublocade during pregnancy should be considered only if the benefits outweigh the risks (see FDA package insert for full details www.accessdata.fda.gov/drugsatfda_docs/label/2017/209819s000lbl.pdf).

Assessment

No evidence clearly predicts which patients are best matched to buprenorphine versus other OUD medications. Thorough assessment helps determine whether buprenorphine treatment is appropriate for a patient. (Part 2 of this TIP covers screening and assessment in more detail.) **Before prescribing buprenorphine:**

- **Check the state prescription drug monitoring program database.**
- **Assess the patient's history.**
  - Conduct a medical, psychiatric, substance use, and substance use treatment history.
  - Assess recent opioid use, including frequency, quantity, type, route, and last day of use.
  - Establish OUD diagnosis.
  - Assess for other substance use disorders (SUDs), including those involving alcohol, benzodiazepines, or stimulants.
- **Conduct a focused physical examination**, refer for a physical exam, or get a record of a recent one.

  - **Assess for signs and symptoms of intoxication.** Do not give a first dose to a patient who is sedated or intoxicated. Assess and treat him or her appropriately.
  - **Assess for evidence of opioid withdrawal and physiological dependence.** The Clinical Opioid Withdrawal Scale (COWS) or the Clinical Institute Narcotic Assessment (CINA) Scale for Withdrawal Symptoms can be used to assess withdrawal signs (see "Resource Alert: Opioid Withdrawal Scales"). The patient should exhibit signs of opioid withdrawal before taking the first dose of buprenorphine to avoid precipitated withdrawal. For example, the Risk Evaluation and Mitigation Strategy (REMS) for buprenorphine indicates that a COWS score of 12 or higher is typically adequate for a first dose. Confirming opioid withdrawal suggests that the patient is physically dependent on opioids and can begin induction with a typical 2 mg/0.5 mg or 4 mg/1 mg buprenorphine/naloxone dose.

- **Obtain laboratory tests.**
  - **Conduct drug and alcohol tests.** Use reliable urine tests for opioids (including morphine, methadone, buprenorphine, and oxycodone), benzodiazepines, cocaine, and other drugs commonly used in the area. Use a breathalyzer to estimate the patient's blood alcohol content. Do not provide buprenorphine until the alcohol reading is considerably below the legal level of alcohol intoxication.
  - **Conduct a pregnancy test.** Transmucosal buprenorphine or methadone maintenance treatment are recommended for OUD in pregnancy.[306] There are limited data regarding use in pregnant women with OUD with the buprenorphine implants and with the extended-release injection formulation. If buprenorphine is used during pregnancy, it should generally be transmucosal monoproduct.[307] Refer pregnant patients to prenatal care.
  - **Assess liver function.** If possible, obtain liver function tests, but do not wait for results before starting transmucosal buprenorphine treatment. A patient with chronic hepatitis can receive OUD treatment with buprenorphine. Discuss risks and benefits if the patient's liver enzymes are at or above five times the normal level and monitor liver function during treatment. Patients with transaminase levels less than five times normal levels, including patients with hepatitis C virus, appear to tolerate buprenorphine well.[308,309] Exhibit 3D.2 gives more information about hepatic impairment and buprenorphine. **Liver function tests should be obtained and reviewed before initiating buprenorphine implants or extended-release buprenorphine because these formulations are long acting.**
  - **Conduct hepatitis and HIV tests.** Hepatitis B and C are common among patients entering buprenorphine treatment. HIV infection is also prevalent. If possible, test the patient for these infections and refer to treatment as appropriate. The Centers for Disease Control and Prevention recommends hepatitis B vaccination for individuals seeking treatment for SUDs.[310]

Resource Alert: Opioid Withdrawal Scales

- The COWS and other opioid withdrawal scales can be downloaded from Annex 10 of WHO's *Guidelines for the Psychosocially Assisted Pharmacological Treatment of Opioid Dependence* from the National Center for Biotechnology Information website (www.ncbi.nlm.nih.gov/books/NBK143183/).
- The CINA Scale for Withdrawal Symptoms is also available online (www.ncpoep.org/wp-content/uploads/2015/02/Appendix_7_Clinical_Institute_Narcotic_Assessment_CINA_Scale_for_Withdrawal_Symptoms.pdf).

Patient Selection

No evidence clearly predicts which patients are best treated with buprenorphine versus other OUD medications. Inform all patients with OUD about treatment with transmucosal buprenorphine and where it's available. (See "Treatment Planning" in Part 2 of this TIP for more on shared decision making.)

Patients who responded well to buprenorphine in the past should be considered for this treatment.

Prior use of diverted buprenorphine doesn't rule out OUD treatment with buprenorphine. Diverted buprenorphine is often associated with an inability to access treatment,[311] and it's often used to self-treat opioid withdrawal rather than to "get high."[312,313]

Unsuccessful treatment experiences with buprenorphine in the past do not necessarily indicate that buprenorphine will be ineffective again. Motivation and circumstances change over time. Also, treatment varies by provider, clinic, and setting, as it does for other medical illnesses. Records from previous providers can contextualize the extent of past treatment.

Pregnant women should be considered for transmucosal buprenorphine treatment.

Stable patients are the best candidates for buprenorphine implants. Implants are indicated for patients who have already achieved illicit opioid abstinence and clinical stability while taking transmucosal buprenorphine for at least 90 days. Their current dose should be 8 mg/day or less.[314] There is no absolute definition of clinical stability, but per the implant package insert, patients may be stable if they are:[315]

- Abstaining currently from illicit opioids.
- Having little or no craving for illicit opioids.
- Living in a stable environment.
- Participating in a structured job or activity.
- Engaging in a positive social support system.
- Lacking recent hospitalizations, emergency department visits, or crisis interventions for substance use or mental illness.
- Adhering to clinic appointments and other aspects of treatment and recovery plans.

> **Do not taper patients to 8 mg daily solely to switch them to implants.**

Informed Consent

Inform all patients of:

- Their OUD diagnosis and the nature of the disorder
- Risks and benefits of all available medications for OUD
- Risks and benefits of nonmedication treatments

Educate patients about basic buprenorphine pharmacology and induction expectations (Exhibit 3D.5). They should understand the need to be in opioid withdrawal that's visible to the prescriber (or for home induction, that meets predefined self-assessment criteria) to avoid precipitated withdrawal.

> **Use language and written materials appropriate to each patient's comprehension level to ensure that he or she understands the options and can make informed decisions.**

Exhibit 3D.5. Key Points of Patient Education for Buprenorphine

Before starting OUD treatment with buprenorphine, patients should:

- Tell providers the prescribed and over-the-counter medications they take, to allow drug interaction assessment.
- Understand the goal of the first week of treatment: To improve withdrawal symptoms without oversedation.
- Tell providers if they feel sedated or euphoric within 1 to 4 hours after their dose.
- Be given the appropriate buprenorphine medication guide.
- Know possible side effects, including:
  - Headache.
  - Nausea.
  - Sweating.
  - Sexual dysfunction.
  - Dizziness.
  - Vomiting.
  - Constipation.
- Agree to store medication securely and out of the reach of others.
- Alert providers if they discontinue medications, start new ones, or change their medication dose.
- Understand that discontinuing buprenorphine increases risk of overdose death upon return to illicit opioid use.
- Know that use of alcohol or benzodiazepines with buprenorphine increases the risk of overdose and death.
- Understand the importance of informing providers if they become pregnant.
- Tell providers if they are having a procedure that may require pain medication.
- Be aware of resources through which to obtain further education for
  - Themselves: *Decisions in Recovery: Treatment for Opioid Use Disorder* (https://store.samhsa.gov/product/SMA16-4993).
  - Their families and friends: *Medication-Assisted Treatment for Opioid Addiction: Facts for Families and Friends* (www.ct.gov/dmhas/lib/dmhas/publications/MAT-InfoFamilyFriends.pdf).

Initiating Buprenorphine Treatment

It can be helpful to use a buprenorphine treatment agreement for patients treated in office-based settings (see Chapter 3D Appendix for a sample treatment agreement).

Induction can occur in the office or at home. Most clinical trials were conducted with office-based induction, and extant guidance recommends this approach.[316] However, office-based induction can be a barrier to treatment initiation. Home induction is increasingly common.[317]

Office-Based Induction

Providers can perform office-based induction by ordering and storing induction doses in the office or by prescribing medication and instructing patients to bring it to the office on the day of induction. **Office-based induction allows providers to:**

- Ensure **that patients know how to take medication** without swallowing or spitting it out if they have too much saliva or experience unpleasant tastes. Tell them to wait to eat or drink until the medication is totally dissolved.
- **Enhance the therapeutic relationship.**
- **Verify the presence of opioid withdrawal and absence of precipitated opioid withdrawal.**
- **Ensure the lack of sedation 1 to 2 hours after the first dose in patients taking sedatives.**
- **Use time between doses for patient self-assessment.** See the Chapter 3D Appendix for sample goal-setting forms that help patients identify treatment goals and triggers for use.

Home Induction

Home induction can be safe and effective.[318] Retention rates are similar to office inductions,[319] but no comparison data from large randomized controlled studies exist. The American Society of Addiction Medicine National Practice Guideline recommends home induction only if the patient or prescriber has experience with using buprenorphine.[320,321] Clinical experience indicates that patients suitable for home induction:

- Can describe, understand, and rate withdrawal.
- Can understand induction dosing instructions.
- Can and will contact their provider about problems.

Educate patients about how to assess their withdrawal, when to start the first dose, how to take the medication properly, and how to manage withdrawal on induction day. Instruct patients to take their first dose when they experience opioid withdrawal at least 12 hours after last use of heroin or a short-acting prescription opioid. Effectively switching from methadone to buprenorphine can be challenging. This should generally be started with office-based induction. Consult with a medical expert knowledgeable about methadone in these situations until experience is gained. Withdrawal can include:

- Goose bumps.
- Nausea.
- Abdominal cramps.
- Running nose.
- Tearing.
- Yawning.

Advise patients to abstain from tobacco before dosing. Many patients with OUD use tobacco products. Nicotine causes vasoconstriction, decreasing the surface area of blood vessels that absorb buprenorphine.

Be available for phone consultation during the induction period and for an in-office evaluation should the need arise. See patients in the office within approximately 7 days of the start of home induction. (See the Chapter 3D Appendix for a sample buprenorphine/naloxone home dosage schedule.)

Induction

Patients who are currently physically dependent on opioids

Patients should begin buprenorphine when they are exhibiting clear signs of opioid withdrawal. Induction typically starts with a 2 mg to 4 mg dose of buprenorphine or a 2 mg/0.5 mg to 4 mg/1 mg dose of buprenorphine/naloxone.[322] Depending on the formulation used and whether a given patient has a dry mouth, the dose can take between 3 and 10 minutes to dissolve fully. After approximately 2 hours, an additional 2 mg to 4 mg dose of buprenorphine/naloxone can be given if there is continued withdrawal and lack of sedation.

Always individualize dosing. The FDA label recommends a maximum buprenorphine/naloxone dose of 8 mg on Day 1 and 16 mg on Day 2.[323] When dosing outside of FDA recommendations, document the clinical rationale, including risks and benefits. Remember that some patients stabilize on lower doses.

If patients experience sedation upon first dose, stop and reevaluate the following:

- Did they recently take other sedating medications (e.g., benzodiazepines)?
- Have they recently been in a controlled environment, such as a hospital, jail, or residential drug treatment facility?
- Was the history of recency and amount of opioid use inaccurate?
- Was the heroin used of poor quality?
- Was their use mostly of low-potency opioids (e.g., codeine)?

Consider whether a dose decrease, change in treatment plan, or both are necessary. If induction is still indicated, adjust the dose more slowly as needed to minimize sedation. The dose can be adjusted on subsequent days to address continued withdrawal or uncontrollable craving if the patient is not sedated.

Patients with a history of OUD who are not currently physically dependent on opioids

Buprenorphine induction can be appropriate for certain patients with a history of opioid addiction at high risk for return to use of opioids but not currently dependent on them. This includes patients who've been incarcerated or in other controlled environments.[324] Before starting treatment, discuss risks and benefits of buprenorphine and other medications (including extended-release naltrexone [XR-NXT]). Buprenorphine doses should begin at lower-than-usual levels (e.g., 1 mg). They should be increased more slowly than in tolerant patients to avoid oversedation and possible overdose. Take particular care with patients who are being treated with other central nervous system depressant medications.[325] At the beginning of treatment, directly administer doses in an OTP or in the office. This will allow patients to be observed for sedation after dosing and will reduce the risk that patients take more medication than prescribed.

In one study, research participants not currently physically dependent on opioids but with a history of OUD were started on 1 mg buprenorphine with weekly 1 mg dose increases to 4 mg, followed by 2 mg weekly increases to 8 mg. Most patients tolerated this dose induction, and the mean daily dose exceeded 8 mg per day by the fifth week, when the planned dose was 6 mg.[326] As with all opioid agonist treatment, dosing should be individualized and based on careful patient assessment during treatment.

Patients who are currently taking methadone

Some patients who take methadone may wish to switch to buprenorphine treatment for a variety of reasons. This often requires methadone dose reduction before switching medications, which may increase the risk of return to opioid use. Exercise caution with this approach and thoroughly discuss the risks and benefits with the patients before embarking on the change in medication. Experienced prescribers should conduct this procedure in the office, not via home induction. The lower the methadone dose and the longer it's been since the last dose, the easier the transition.

Before initiating buprenorphine, carefully taper methadone to lower the risk of return to illicit opioid use during transition. Patients who take methadone for OUD should taper to 30 mg to 40 mg methadone per day and remain on that dose for at least 1 week before starting buprenorphine.[327] With patients' permission, OTPs can confirm the time and amount of patients' last methadone dose.

Do not start buprenorphine until the patient manifests signs of opioid withdrawal. At least 24 hours should pass between the last dose of methadone and the first dose of buprenorphine. Waiting 36 hours or more reduces risk of precipitated withdrawal. Lower doses of buprenorphine/naloxone are less likely to precipitate methadone withdrawal.[328] For example, once opioid withdrawal is verified, an initial dose of 2 mg/0.5 mg can be given. If patients continue to have unrelieved opioid withdrawal after the first 2 mg dose, administer another 2 mg/0.5 mg dose approximately every 2 hours as needed (holding for sedation). Induction should be conducted slowly; consider palliating unrelieved withdrawal with nonopioid therapies for the first few days of transition to buprenorphine. Be alert to any increase in withdrawal symptoms, as this may suggest precipitated withdrawal.

Dose Stabilization

Stabilization occurs when there is evidence of:

- Markedly reduced or eliminated illicit opioid use.
- Reduced craving.

- Suppression of opioid withdrawal.
- Minimal side effects.
- Patient-reported blunted or blocked euphoria during illicit opioid use.

Remind patients to take their dose once daily rather than splitting it.

Document reduced illicit drug use via patient self-report and urine drug testing. Consecutive negative urine test results suggest a positive prognosis.

Continue monitoring dose effectiveness during early stabilization. Dose adjustments may still be necessary (Exhibit 3D.6). Buprenorphine treatment should substantially reduce opioid cravings. See Chapter 3E: Medical Management Strategies for detailed information on the management of patients taking buprenorphine in office-based treatment settings.

Exhibit 3D.6. Adjusting the Buprenorphine Dose

When to increase the dose:

- Are patients taking medication correctly and as scheduled?
  - If they take at least 16 mg per day, mu-opioid receptors are approximately 80 to 95 percent occupied.[329]
  - If there are adherence problems, assess causes and intervene to promote adherence and proper administration (e.g., offer supervised dosing at the clinic, by a network support, at a pharmacy).
  - **If patients are taking doses correctly, a dose increase may be indicated, if certain conditions exist.**
- Are patients taking other medications that may interfere with buprenorphine metabolism?
- If patients are taking doses properly**, increase the dose if they still have opioid withdrawal** (document with a clinical tool like COWS), **opioid craving, or "good" effects (e.g., feeling "high") from using illicit opioids.**
  - **Craving can be a conditioned response.** It may not decrease with dose increases if patients spend time with people who use opioids in their presence.
  - Dose increases typically occur in 2 mg to 4 mg increments.
  - It will take about 5 to 7 days to reach steady-state plasma concentrations after a dose increase.
  - **Offer psychosocial referrals to help decrease and manage cravings.**
- **Determine whether nonpharmacological problems are contributing to the need for increase.**
  - For example, do patients show signs and symptoms of untreated major depressive or generalized anxiety disorders? Are they living in a chaotic household? Do they have childcare problems or financial difficulties? Are they experiencing trauma or trauma-related mental disorders?
  - **Address or refer to counseling to address these problems.**

When to decrease the dose:

- Decrease the dose **when there is evidence of dose toxicity** (i.e., sedation or, rarely, clearly linked clinically relevant increases in liver function tests).
- Hold the dose **when there is acute alcohol or benzodiazepine intoxication.**

Once patients have stabilized, continue to screen and evaluate for mental disorders and psychosocial problems that may need to be addressed (e.g., having a spouse or cohabitant who is using illicit opioids). Support patients' engagement in prosocial activities and progress toward treatment goals and recovery as they decrease use of illicit substances.

Offer referrals for adjunctive counseling and recovery support services as needed. It may not be possible to eliminate opioid craving completely, regardless of the dose. Counseling can help patients reduce and manage craving. A more important measure of dose adequacy than craving is whether patients report that the feeling of euphoria associated with self-administered illicit opioids is blunted or

blocked. **Patients who were not interested in adjunctive addiction or mental health counseling during induction may become receptive to it when they are feeling more stable.**

Be cautious when increasing doses above 24 mg/6 mg per day. Nearly all patients stabilize on daily doses of 4 mg/1 mg to 24 mg/6 mg. Very limited data show additional benefits of doses higher than the FDA label's recommended maximum of 24 mg/6 mg.[330] Carefully document clinical justification for higher doses, and always have a diversion control plan in place. Doses above 24 mg/6 mg a day may unintentionally heighten diversion risk. Patients not responding to high doses of buprenorphine at the upper limit approved by FDA should be considered for methadone treatment.

Risk Evaluation and Mitigation Strategy

Practitioners should **become familiar with the FDA-approved REMS for buprenorphine**. It provides useful information and checklists for providers. REMS can be found online for:

- Buprenorphine monoproduct and buprenorphine/naloxone (www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=IndvRemsDetails.page&REMS=352)
- Transmucosal buprenorphine (www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=RemsDetails.page&REMS=9).
- Buprenorphine implants (www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=IndvRemsDetails.page&REMS=356) .
- Buprenorphine extended-release injection (www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=indvremsdetails.page&rems=376).

See also "Buprenorphine Induction and Maintenance Appropriate Use Checklists" in Chapter 3D Appendix.

Transmucosal Buprenorphine Dosing Summary

Induction and stabilization

The goal is to reduce or eliminate opioid withdrawal and craving without causing sedation:

- Induction and stabilization strategies can vary based on patient variables and use of short- versus long-acting opioids. For more discussion on induction models, see the Providers' Clinical Support System's Models of Buprenorphine Induction (http://pcssmat.org/wp-content/uploads/2015/01/Models-of-Buprenorphine-Induction.pdf).
- The combination buprenorphine/naloxone product is safe to use for induction for most patients.
- The buprenorphine monoproduct (without naloxone) has been recommended for the treatment of pregnant women[331] because of the danger to the fetus of precipitated opioid withdrawal if the combination product were to be injected. Although there are some publications with small sample sizes that indicate that the combination product appears to be safe in pregnancy,[332,333] the safety data are insufficient at this time to recommend its use.[334] This is an area of some uncertainty. An expert panel on the treatment of OUD in pregnancy was unable to agree whether pregnant women should be treated with the monoproduct or combination product.[335]
- Prescribers should observe the patient taking the medication to ensure proper use, especially if the patient is new to buprenorphine treatment. It can be helpful to do this periodically after induction, especially when the prescribed dose is not providing the expected benefit.

- Before the first dose, the patient should be in opioid withdrawal (to avoid precipitated withdrawal).
- The first dose is typically 4 mg/1 mg (2 mg if withdrawal is from methadone).
- Repeat dose as needed for continuing withdrawal every 2 hours up to typically 8 mg on the first day.

At the start of the next day, patients typically take the first day's total dose all at once:

- If necessary, an additional 2 mg to 4 mg can be given every 2 hours up to approximately a 16 mg total daily dose to treat continuing opioid withdrawal and craving on Day 2 or 3, barring sedation.
- The initial stabilization dose can often be achieved within the first several days of treatment.

Maintenance

Typical maintenance doses range from 4 mg/1 mg to 24 mg/6 mg per day. An effective maintenance dose is the lowest dose that can:

- Eliminate withdrawal.
- Reduce or eliminate opioid craving.
- Reduce or stop illicit opioid use's desirable effects.
- Be well tolerated (e.g., not produce sedation).

Duration of treatment

- Treatment should last for as long as patients benefit from treatment.
- Longer treatment length is associated with positive treatment outcomes.

Initiation of Buprenorphine Implants

Prescribers and implanters of buprenorphine implants require special certification to make this formulation available to their patients. In addition, implanters must get special training in the Probuphine REMS program to obtain certification to implant and remove this formulation. After completing training, providers can order implants through a central pharmacy for delivery, along with an implant insertion kit that contains all necessary implant procedure materials except a local anesthetic. If the prescriber is not performing the procedure, the prescriber should ensure that the implanter has completed the required training. For more information, see the Probuphine REMS program webpage (http://probuphinerems.com/probuphine-locator/).

The prescriber and implanter/remover must record the number of implanted/removed rods and their serial numbers and location, the date of the implant, and who performed the procedure. The implanter should document implant and inspection procedures, as with any other standard procedure.

Instruct patients to take the last transmucosal dose of buprenorphine 12 to 24 hours before insertion. Remind them to shower and thoroughly wash the nondominant arm, which is preferred for insertion.

Implant procedure

Subdermal insertion of the four rods takes less than 30 minutes. Local anesthetic (lidocaine) is typically used. The implant procedure includes the following steps:

- Provide education about what to expect during the procedure.
- Obtain appropriate consent form(s).
- Provide a local anesthetic (e.g., lidocaine).

- Using sterile procedures, make a single incision in the inner upper arm between the biceps and triceps muscles, about 8 cm to 10 cm from the medial epicondyle.
- Using a cannula and an obturator, insert rods serially, pivoting the cannula slightly after each rod insertion in the subdermal space so that the rods lie next to one another, nearly parallel in a fanlike pattern.
- After implantation, apply butterfly strips and a pressure bandage.
- **Review wound care with the patient,** and provide a copy of the instructions.
- **Advise the patient not to drive or engage in heavy physical activity** for approximately 24 hours.
- **Do not give the patient a prescription for transmucosal buprenorphine** at this time.

Wound care

The patient should return within 1 week of the implant procedure for a wound care check. Check for signs of infection, trouble healing, or implant extrusion. The rods are subdermal, so they should remain palpable. Document that all four rods were palpated.

Stabilization

Maintain contact with patients after implant placement. Even among highly stable patients, return to illicit opioid use can occur. Explain the risk of unintentional overdose if patients return to illicit opioid or alcohol or benzodiazepine use while implants are in place. It is important to monitor the patient between implant placements.

Schedule office visits no less than once a month for continued assessment of maintenance of stability, manual palpation of the four implanted rods, and ongoing psychosocial support and counseling per the FDA label (www.accessdata.fda.gov/drugsatfda_docs/label/2016/204442Orig1s000lbl.pdf). If the patient returns to illicit opioid use, consider whether adequate psychosocial treatment has been given.

Consider transmucosal medication supplementation if a patient with implants destabilizes and reports inadequate opioid blockade. In one study,[336] 17.9 percent of participants with buprenorphine implants needed supplemental sublingual buprenorphine/naloxone. Most required small doses, such as 2 mg/0.5 mg per day. Consider more frequent assessment and higher intensity of treatment for patients who continue using illicit opioids or other substances.

Removal

After 6 months, have a certified implanter remove them. Implantation of a second set of rods in the opposite arm can then occur. There is no experience with inserting additional implants into other sites or second insertion into a previously used arm. After one insertion in each arm, most patients should transition to a transmucosal buprenorphine-containing product for continued treatment. Patients should follow the same directions to prepare for implant removal as they did for insertion. The removal procedure may require stitches. Patients should visit the clinic for removal of stitches and wound assessment within 1 week of removal. Store and dispose of rods safely in accordance with local and federal regulations.

Initiation of Buprenorphine Extended-Release Injection

Healthcare settings and pharmacies need special certification to order and dispense extended-release injectable buprenorphine to ensure long-acting preparations are dispensed directly to healthcare providers for administration and by healthcare providers to patients (see www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=indvremsdetails.page&rems=376 for more details).

Before initiating extended-release buprenorphine treatment, patients with moderate-to-severe OUD should be stabilized on transmucosal buprenorphine (8 mg to 24 mg daily) for at least 7 days. Do not use in opioid-naïve patients. Obtain liver function and pregnancy tests. Extended-release buprenorphine is not recommended for patients with severe hepatic impairment and may not be appropriate for patients with moderate hepatic impairment because of the long-acting nature of this formulation. There are insufficient data on its use in pregnancy to recommend initiating this formulation during pregnancy.

Inform patients that:

- The medication is only available in a restricted program (the Sublocade REMS program) via specific pharmacies and healthcare providers, as intravenous self-injection by patients can cause death.
- After abdominal injection, a lump may be present at the injection site for a few weeks. It will get gradually smaller. Patients should not rub or massage it or let belts or waistbands rub against it.
- Patients should tell their healthcare providers that they are being treated with this medication.
- Using alcohol, benzodiazepines, sleeping pills, antidepressants, or some other medications with extended-release buprenorphine can lead to drowsiness or overdose.
- The most common side effects are constipation, headache, nausea, vomiting, increased liver enzymes, tiredness, and injection site itching or pain.
- Patients should inform their provider if they become pregnant during treatment with this formulation. They should have a risk/benefit discussion about continuing with this formulation given the limited safety data on its impact on the developing fetus. They should be informed that their newborn can have symptoms of opioid withdrawal at birth.

Storage

Follow package insert directions for medication storage under refrigeration. Keep at room temperature for at least 15 minutes before injection (discard if left at room temperature for more than 7 days).

Administration

Rotate the abdominal subcutaneous injection site with each injection, following the instructions in the package insert. Record the location of each injection in the medical record. Each of the first two monthly doses (with at least 26 days between doses) should be 300 mg. Subsequent monthly doses should be 100 mg. Some patients may benefit from increasing the maintenance dose to 300 mg monthly if they have tolerated the 100 mg dose but continue to use illicit opioids.

Medical management

Monitor patient progress and response to treatment during regular office visits and with periodic urine drug testing. Examine the injection site for reactions, infections, or evidence of attempts to remove the depot medication. If the medication is discontinued, the patient should continue to be seen and evaluated for several months for sustained progress in treatment and for signs and symptoms of opioid withdrawal, which should be treated as clinically appropriate.

Duration of Buprenorphine Treatment

There is no known duration of therapy with buprenorphine (or methadone or XR-NTX) after which patients can stop medication and be certain not to return to illicit opioid use. Those who stay in treatment often abstain longer from illicit opioid use and show increasing clinical stability. Long-term treatment outcomes up to 8 years after buprenorphine treatment entry show lower illicit opioid use among those with more time on medication.[337]

Patients should take buprenorphine as long as they benefit from it and wish to continue.

Given the often-chronic nature of OUD and the potentially fatal consequences of unintended opioid overdose, it's critical that you **base patients' length of time in treatment on their individual needs.**

Successful Buprenorphine Treatment

The goal of buprenorphine treatment is full remission from OUD. Maintaining illicit opioid abstinence is ideal, but imperfect abstinence does not preclude treatment benefits. Patients should do better in treatment than before treatment. If not, seek alternatives.

Do not judge treatment progress and success on the amount of medication a patient needs or how long treatment is required. Rather, gauge treatment progress and success based on patients' achievement of specific goals that were agreed on in a shared decision-making and treatment planning process.

Consider this analogy: A patient with poorly controlled diabetes was previously unable to work and was admitted to the hospital several times for diabetic ketoacidosis. When taking insulin regularly, the patient worked part time, had fewer hospitalizations for diabetic ketoacidosis despite a nondiabetic diet, and had lower (but still high) hemoglobin A1C. This patient's treatment with insulin is not a "failure" because perfect control and function were not restored, and the patient would not be discharged from care against his or her will.

Dose Tapering and Buprenorphine Discontinuation

Following short-term medically supervised withdrawal, patients frequently restart illicit opioid use.[338] In contrast to short-term medically supervised withdrawal, dose tapering refers to gradually reducing the buprenorphine dose in patients who have been stabilized on the medication for some time.

Base decisions to decrease dose or stop buprenorphine on patients' circumstances and preferences. Successful dose reductions may be more likely when patients have sustained abstinence from opioids and other drugs, psychosocial support, housing, effective coping strategies, stable mental health, employment, and involvement in mutual-help programs or other meaningful activities.[339] However, there is no guarantee that even patients with years of abstinence, full-time employment, stable housing, and psychosocial supports can remain abstinent after discontinuing buprenorphine.

It is up to patients to decide whether to taper or eventually discontinue medication. Help them make informed choices by educating them about the process and fully including them in decision making. Invite them to reenter treatment if they believe they may return or have already returned to opioid use.

Before beginning to taper the dose of medication, explore these considerations with patients:

- **How have they responded to treatment so far?** Are they in full remission from OUD? Do they have adequate mental and social supports to remain in remission and maintain recovery?

- **Why do they want to taper?** They may be motivated by inconvenience, expense, loss of insurance coverage, side effects, feelings of shame, pressure from family, and lack of recovery supports. Many of these reasons are not predictive of a successful outcome.
- **What do they expect to be different** after tapering or discontinuing buprenorphine?
- **Do they understand the risks and benefits** of dose decrease and discontinuation of buprenorphine?
- **What strategies do they have for engaging family members and recovery supports to reduce the risk of return to illicit substance use?**
- **Do they grasp the risk of overdose associated with a return to illicit opioid use?**
- **Do they have a safety plan?** To reduce overdose risk after a return to use, plans should include:
  - A prescription for naloxone or a naloxone kit.
  - Instructions on recognizing and responding to an overdose.
  - Information on naloxone use for family and members of the patient's recovery support network.
  - See SAMHSA's *Opioid Overdose Prevention Toolkit* (https://store.samhsa.gov/shin/content/SMA16-4742/SMA16-4742.pdf) for more guidance.
  - If patients return to opioid use, it may be appropriate for them to restart buprenorphine or switch to methadone or XR-NTX treatment. These options should be discussed with them.

- **Have they thought about how they will feel if they attempt to taper off of medication but cannot do so?** Convey to patients that the inability to taper is not a failure and that they should not be afraid or embarrassed to discuss stopping the taper.

Document the discussion, patient education, and decision in the medical record.

There is no ideal tapering protocol. Providers and patients should understand this before beginning a taper. Whether buprenorphine is ultimately discontinued, patients need additional psychosocial and recovery support during this time. Generally, taper occurs over several months to permit patients to acclimate to the lower dose and to reduce potential discomfort from opioid withdrawal and craving.

For patients who wish to discontinue buprenorphine, national and international guidelines recommend gradual dose reductions and advice to patients that they can stop the taper at any time.[340,341,342]

Consider increased monitoring and proactive discussions about how to address and manage cravings and withdrawal symptoms. Taper protocols vary in duration and may include use of ancillary medication, such as clonidine, if needed (Exhibit 3A.2).[343]

Continue to monitor patients who successfully taper off buprenorphine completely. Establish a post-taper monitoring and support plan (see Chapter 3E for more information on medical management strategies). Continue to assess and monitor patients' progress and how they cope with stress and triggers to use. Discuss the role of XR-NTX in preventing return to opioid use after completing treatment with an opioid agonist (see Chapter 3C for more information on naltrexone).

Chapter 3D Appendix

Buprenorphine Induction and Maintenance Appropriate Use Checklists

Patient Name: _____

BTOD|REMS

APPROPRIATE USE CHECKLIST:
BUPRENORPHINE-CONTAINING TRANSMUCOSAL PRODUCTS FOR OPIOID DEPENDENCE

This checklist is a useful reminder of the safe use conditions and monitoring requirements for prescribing buprenorphine-containing transmucosal products for opioid dependence.

Requirements to address during each patient's appointment include:

- understanding and reinforcement of safe use conditions
- the importance of psychosocial counseling
- screening and monitoring patients to determine progress towards treatment goals

If a patient continues to abuse various drugs or is unresponsive to treatment, including psychosocial intervention, it is important that you assess the need to refer the patient to a specialist and/or a more intensive behavioral treatment environment.

Additional resource: Physician Clinical Support System: http://pcssb.org/

This checklist may be used during the induction period and filed in patient's medical record to document safe use conditions. Once a maintenance dose has been established, use the maintenance checklist.

MEASUREMENT TO ENSURE APPROPRIATE USE	NOTES
Date:	
INDUCTION	
☐ Verified patient meets appropriate diagnostic criteria for opioid dependence	
☐ Discussed risks described in professional labeling and Medication Guide with patient	
☐ Explained or reviewed conditions of safe storage of medication, including keeping it out of the sight and reach of children	
☐ Provided induction doses under appropriate supervision	
☐ Prescribed limited amount of medication at first visit	
☐ Scheduled next visit at interval commensurate with patient stability • Weekly, or more frequent visits recommended for the first month	

Patient Name: _____

BTOD|REMS

APPROPRIATE USE CHECKLIST:

BUPRENORPHINE-CONTAINING TRANSMUCOSAL PRODUCTS FOR OPIOID DEPENDENCE

This checklist may be used for visits following the induction period and filed in patient's medical record to document safe use conditions.

MEASUREMENT TO ENSURE APPROPRIATE USE	NOTES
Date: **Visit #**	
MAINTENANCE	
☐ **Assessed and encouraged patient to take medication as prescribed** • Consider pill/film count/dose reconciliation	

☐ **Assessed appropriateness of dosage**
• Buprenorphine combined with naloxone is recommended for maintenance:
  • Buprenorphine/Naloxone SL tablet and film (Suboxone®): doses ranging from 12 mg to 16 mg of buprenorphine are recommended for maintenance
  • Buprenorphine/Naloxone SL tablet (Zubsolv®): a target dose of 11.4 mg buprenorphine is recommended for maintenance
  • Buprenorphine/Naloxone Buccal Film (Bunavail®): a target dose of 8.4 mg of buprenorphine is recommended for maintenance
• Doses higher than this should be an exception
• The need for higher dose should be carefully evaluated	

☐ **Conduct urine drug screens as appropriate to assess use of illicit substances**	
☐ **Assessed participation in professional counseling and support services**	
☐ **Assessed whether benefits of treatment with buprenorphine-containing products outweigh risks associated with buprenorphine-containing products**	
☐ **Assessed whether patient is making adequate progress toward treatment goals** • Considered results of urine drug screens as part of the evidence of the patient complying with the treatment program • Consider referral to more intensive forms of treatment for patients not making progress	
☐ **Scheduled next visit at interval commensurate with patient stability** • Weekly, or more frequent visits are recommended for the first month	

Sample Goal Sheet and Coping Strategies Form

Goals are things you would like to accomplish.

Date: _____ Patient Name: _____

3-Month Goals

1._____

_____

2._____

_____

3._____

_____

6-Month Goals

1._____

_____

2._____

_____

3._____

_____

1-Year Goals

1._____

_____

2._____

_____

3._____

_____

List of Triggers to Using Drugs

_____

_____

People to Stay Away From

_____

_____

Places to Stay Away From

_____

_____

Ways To Cope or Manage Stress Without Using Drugs

_____

_____

M. Lofwall, February 27, 2017 (personal communication). Adapted with permission.

Available online (www.accessdata.fda.gov/drugsatfda_docs/rems/BTOD_2017-01-23_Appropriate_Use_Checklist.pdf).
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Buprenorphine/Naloxone Home Dosage Schedule: Films or Tablets

Name: _____ **Date:** _____

Procedure for taking buprenorphine:

- Let the medication dissolve under your tongue for at least 10 minutes. Do not suck on it.*
- Do not eat, drink, or smoke cigarettes for 30 minutes after you take your medication.
- Wait 2 hours between each dose.

The maximum dose is 16 mg/4 mg. If you reach this dose, you cannot increase further without calling the office first. The office phone number is _____ [insert phone number].

Day 1 Induction Day (In Office): You have taken a total dose of _____ mg.

Day 2 in the Morning: Take the total dose you took on **Day 1** = _____ mg.

- If you experience withdrawal 2 hours later, you may take one 2 mg/0.5 mg film or tablet.
- Record your withdrawal symptoms: _____.
- If you continue to experience withdrawal 2 hours later, you may take one more 2 mg/0.5 mg film or tablet or ¼ of an 8 mg/2 mg film or tablet.
- Record your withdrawal symptoms: _____.

Your total dose on **Day 2 cannot** exceed _____ mg. Record your total dose on **Day 2**: _____ mg.

Day 3 in the Morning: Take the total dose you took on **Day 2** = _____ mg.

- If you experience withdrawal 2 hours later, you may take one more 2 mg/0.5 mg film or tablet.
- Record your withdrawal symptoms: _____.
- If you continue to experience withdrawal 2 hours later, you may take one more 2 mg/0.5 mg film or tablet.
- Record your withdrawal symptoms: _____.

Your total dose on **Day 3 cannot** exceed _____ mg. Record your total dose on **Day 3**: _____ mg.

Day 4 in the Morning: Take the total dose you took on **Day 3** = _____ mg.

- If you experience withdrawal 2 hours later, you may take one more 2 mg/0.5 mg film or tablet.
- Record your withdrawal symptoms: _____.
- If you continue to experience withdrawal 2 hours later, you may take one more 2 mg/0.5 mg film or tablet.
- Record your withdrawal symptoms: _____.

Your total dose on **Day 4 cannot** exceed _____ mg. Record your total dose on **Day 4**: _____ mg.

Day 5 to next visit: In the morning, take the total dose you took on **Day 4** = _____ mg.

General Rules

- The maximum dose is 16 mg/4 mg. If you reach this dose, you cannot increase further without calling the office first. The office phone number is _____ [insert phone number].
- Please call if you have any questions. There are no "stupid" questions.
- Call us if you feel sleepy after your dose.
- Please bring this record to your next visit.
- It's okay to take Tylenol (acetaminophen) or Motrin (ibuprofen) for aches/pains.

BRING THIS WITH YOU TO YOUR NEXT APPOINTMENT, scheduled for _____ [insert date and time].

Notes:

*If prescribing the buccal film, ensure the patient understands that the buccal film is placed on the inner cheek (buccal mucosa) rather than sublingually (under the tongue).

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Sample Goal-Setting Form

Name: Date:

Category	**Current Situation Score** (10 = major problems and 0 = no problems).	**What Would Need To Change To Decrease This Score?**	**Priority Score** (10 = highest priority ["I really want to work on this."] and 1 = lowest priority ["I really do not want to work on this.").
Opioid Use			
Other Illicit Drug Use: _____			
Alcohol Use			
Tobacco Use			
Physical Health			
Mental Health			
Legal/Court Issues			
Finances			
Job/Employment			
Hobbies			
Family Relations			
Partner Relations			
Supportive Drug-Free Network			
Education			
Keeping Medication Safe (e.g., not giving it away, selling it, having it stolen)			
Other:			
Other:			

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Buprenorphine Treatment Agreement

This form is for educational/informational purposes only. It doesn't establish a legal or medical standard of care. Healthcare professionals should use their judgment in interpreting this form and applying it in the circumstances of their individual patients and practice arrangements. The information provided in this form is provided "as is" with no guarantee as to its accuracy or completeness.

Treatment Agreement

I agree to accept the following treatment contract for buprenorphine office-based opioid addiction treatment:

1. The risks and benefits of buprenorphine treatment have been explained to me.
2. The risks and benefits of other treatment for opioid use disorder (including methadone, naltrexone, and nonmedication treatments) have been explained to me.
3. I will keep my medication in a safe, secure place away from children (for example, in a lockbox). My plan is to store it [describe where and how].

Buprenorphine Treatment Agreement

4. I will take the medication exactly as my healthcare provider prescribes. If I want to change my medication dose, I will speak with my healthcare provider first. Taking more medication than my healthcare provider prescribes or taking it more than once daily as my healthcare provider prescribes is medication misuse and may result in supervised dosing at the clinic. Taking the medication by snorting or by injection is also medication misuse and may result in supervised dosing at the clinic, referral to a higher level of care, or change in medication based on my healthcare provider's evaluation.
5. I will be on time to my appointments and respectful to the office staff and other patients.
6. I will keep my healthcare provider informed of all my medications (including herbs and vitamins) and medical problems.
7. I agree not to obtain or take prescription opioid medications prescribed by any other healthcare provider without consulting my buprenorphine prescriber.
8. If I am going to have a medical procedure that will cause pain, I will let my healthcare provider know in advance so that my pain will be adequately treated.
9. If I miss an appointment or lose my medication, I understand that I will not get more medication until my next office visit. I may also have to start having supervised buprenorphine dosing.
10. If I come to the office intoxicated, I understand that my healthcare provider will not see me, and I will not receive more medication until the next office visit. I may also have to start having supervised buprenorphine dosing.
11. I understand that it's illegal to give away or sell my medication; this is diversion. If I do this, my treatment will no longer include unsupervised buprenorphine dosing and may require referral to a higher level of care, supervised dosing at the clinic, and/or a change in medication based on my healthcare provider's evaluation.
12. Violence, threatening language or behavior, or participation in any illegal activity at the office will result in treatment termination from the clinic.
13. I understand that random urine drug testing is a treatment requirement. If I do not provide a urine sample, it will count as a positive drug test.
14. I understand that I will be called at random times to bring my medication container into the office for a pill or film count. Missing medication doses could result in supervised dosing or referral to a higher level of care at this clinic or potentially at another treatment provider based on my individual needs.
15. I understand that initially I will have weekly office visits until I am stable. I will get a prescription for 7 days of medication at each visit.
16. I can be seen every 2 weeks in the office starting the second month of treatment if I have two negative urine drug tests in a row. I will then get a prescription for 14 days of medication at each visit.
17. I will go back to weekly visits if I have a positive drug test. I can go back to visits every 2 weeks when I have two negative drug tests in a row again.
18. I may be seen less than every 2 weeks based on goals made by my healthcare provider and me.
19. I understand that people have died by mixing buprenorphine with alcohol and other drugs like benzodiazepines (drugs like Valium, Klonopin, and Xanax).
20. I understand that treatment of opioid use disorder involves more than just taking medication. I agree to comply with my healthcare provider's recommendations for additional counseling and/or for help with other problems.
21. I understand that there is no fixed time for being on buprenorphine and that the goal of treatment is for me to stop using all illicit drugs and become successful in all aspects of my life.
22. I understand that I may experience opioid withdrawal symptoms when I stop taking buprenorphine.
23. I have been educated about the other two FDA-approved medications used for opioid dependence treatment, methadone and naltrexone.
24. I have been educated about the increased chance of pregnancy when stopping illicit opioid use and starting buprenorphine treatment and been informed about methods for preventing pregnancy

Other specific items unique to my treatment include:

Patient Name (print): _____ Patient Signature: _____ Date: _____

This form is adapted from ASAM's Sample Treatment Agreement, which they will update periodically; their most current version of the agreement is available online (www.asam.org/docs/default-source/advocacy/sample-treatment-agreement30fa159472bc604ca5b7ff000030b21a.pdf?sfvrsn=0).

Adapted with permission.[345]

Patient Urine Drug Screen and Medication Count Monitoring Form

Patient Name: _____

Dates To Be Called: _____

Called for:

□ Urine Drug Screen

□ Medication Count at □Office or □Pharmacy FOR:

□ Buprenorphine/Naloxone

□ Other (list drug: _____, _____, _____)

Documentation of Phone Call to Patient

Patient was called at _____ (insert phone #) on _____ (date) at ___:___ (time) and informed of monitoring required (described above) within the next _____ hours.

Check One:

□ I spoke with patient

□ Message left on answering machine/voicemail

□ Message left with _____

□ Other _____

Signature of Staff Member Making Phone Call: _____

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Pharmacy Tablet/Film Count Form

(Note: Before sending this form, discuss with the pharmacist to explain goals and procedures and to ensure agreement and understanding.)

Date: _____

To: Pharmacists @ _____ Pharmacy

From: Healthcare Provider: _____
Clinic Address: _____
Phone Number: _____

My patient, _____, is starting office-based buprenorphine treatment for opioid dependence.

As part of monitoring this treatment, we ask the patient to do buprenorphine tablet/film counts at random times (we call the patient when it's time for a pill/film count).

The above-named patient lives much closer to your pharmacy than to our treatment clinic. It would be a big help to me and this patient if you would be able to perform periodic tablet/film counts on his/her buprenorphine and then fax this form to us.

On the days we call the patient for a random tablet/film count, the patient would come to your pharmacy with his or her pill bottle. When we call the patient to go for a random tablet/film count, we will fax this form to you. We would appreciate if you could record the tablet/film count results on this form and fax it back to us the same day. This would be a real help to me in monitoring my patient's treatment and also a great service to the patient.

Thank you very much for your help with this! Sincerely,

_____

Buprenorphine/Naloxone Formulation: _____
Dose per Tablet/Film: _____
Total # of tablets/films remaining in bottle: _____
Fill date on bottle: _____
Total # of tablets/films dispensed on fill date: _____
Tablet/film count correct? □ Yes □ No

Please fax this back to: _____

Thank You!

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Chapter 3E: Medical Management Strategies for Patients Taking OUD Medications in Office-Based Settings

Management of patients taking medications for opioid use disorder (OUD) varies by setting. Once patients in office-based opioid treatment (OBOT) stabilize on buprenorphine or naltrexone, providers focus on medication management and treatment of other substance use, medical comorbidities, and psychosocial needs. Treatment of comorbid conditions should be offered onsite or via referral and should be verified as having been received.

Exhibit 3E.1 addresses use of terminology in this chapter.

Exhibit 3E.1. Key Terms

In addition to the key terms defined on page 2 of Part 3 of this Treatment Improvement Protocol (TIP), these terms appear in Chapter 3E:

Psychosocial support: Ancillary services to enhance a patient's overall functioning and well-being, including recovery support services, case management, housing, employment, and educational services.

Psychosocial treatment: Interventions that seek to enhance patient's social and mental functioning, including addiction counseling, contingency management, and mental health services.

Patient Selection

To assess patients' chances of success with standard office-based treatment, consider:

- **Concurrent substance use disorder (SUD) involving alcohol or benzodiazepines.** Benzodiazepine (illicit and prescription) and alcohol use are common in patients with OUD. This use presents clinical challenges, including increased risk of respiratory depression and unintentional overdose or death. Some patients may have taken appropriately prescribed benzodiazepines for years with limited or no evidence of misuse. For such patients, tapering benzodiazepines may be contraindicated and unrealistic. Others may require treatment for a benzodiazepine use disorder. (See Exhibit 3B.1 for strategies for assessing and managing patients in OUD treatment who have concurrent benzodiazepine use disorder).

  Although concomitant use of buprenorphine with benzodiazepines increases the risk of an adverse reaction including overdose death, opioid agonist treatment should not be denied to patients solely because they take benzodiazepines,[346] because untreated OUD can pose a greater risk of morbidity and mortality. The Food and Drug Administration (FDA) advises that careful medication management by healthcare professionals can reduce risk (see www.fda.gov/Drugs/DrugSafety/ucm575307.htm for more information).

Chapter 3E examines key issues in medical management of patients who are prescribed buprenorphine or naltrexone in OBOT settings. It covers regulatory and administrative concerns specific to buprenorphine and naltrexone that affect medical management of patients in office settings.

Approaches to addressing concurrent benzodiazepine use include:

- Get patients' permission to contact their benzodiazepine prescribers to confirm their histories. Speaking with close family members or friends (with patients' permission) can also help in evaluating evidence of alcohol or benzodiazepine misuse (e.g., intoxication, accidents, withdrawal seizures).
- Make sure patients understand that combining buprenorphine with alcohol, benzodiazepines, or other central nervous system depressants risks potential respiratory depression and unintentional overdose death.[347] Overdose death with buprenorphine is most often associated with intravenous benzodiazepine and heavy alcohol use.
- For patients misusing benzodiazepines (e.g., taking in high doses, bingeing, or using intravenously), the TIP expert panel recommends referral to higher-intensity addiction treatment with medically supervised benzodiazepine withdrawal if available (e.g., intensive outpatient programs, residential treatment). Do not rule out concurrent use of buprenorphine or extended-release injectable naltrexone (XR-NTX) for treatment of OUD in more structured settings for these patients.
- For patients who are physically dependent on illicit benzodiazepines but do not inject or binge, a gradual outpatient medically supervised withdrawal can be attempted using long-acting benzodiazepines, under certain conditions that promote safety and reduce risk. These conditions may include:
    - Requiring frequent office visits with observation of patients taking medication.
    - Having significant others monitor patients and report back to the office.
    - Offering a short-duration prescription supply.
    - Monitoring prescription drug monitoring program (PDMP) reports more frequently.
    - Conducting frequent urine tests.
    - Using written treatment agreements outlining conditions for dual buprenorphine and benzodiazepine prescriptions.
- Review patient progress regularly; adjust treatment plans as needed. Document treatment decisions, as research showing the effectiveness and safety of these approaches is lacking.[348]

- **Significant comorbid mental illness or suicidal or homicidal ideation.** Patients who are actively suicidal, homicidal, severely depressed, or psychotic or who are having other significant psychiatric problems may need assessment and treatment by a mental health professional who can treat both the psychiatric comorbidity and the OUD. Depending on the severity, they may need higher levels of mental health services in a crisis center, emergency department, or inpatient setting. An addiction psychiatrist can treat such patients upon discharge.
- **Significant medical comorbidity, including infections.** Severe abscesses, endocarditis, or osteomyelitis from injecting drugs may require hospitalization. If hospitalization is necessary, buprenorphine can be initiated.[349] Initiation of HIV and hepatitis C virus treatments do not contraindicate buprenorphine treatment.[350]

Patient Management and Treatment Monitoring

Base management of OUD on a comprehensive assessment that is updated throughout treatment (see Part 2 of this TIP for more information on conducting assessments). Tailor the management approach to patients' needs and goals. Components of the management approach include:

- The length and frequency of office visits.

- The length of time between prescriptions or XR-NTX injections.
- The frequency of drug testing.
- Ancillary psychosocial and medical treatments and referrals.

Course of Treatment

The typical course of OUD treatment is varied. There is often not a direct pathway from heavy illicit opioid use to no illicit opioid use.[351] Some patients have only occasional returns to use and do not require reinduction on buprenorphine or naltrexone. Other patients may return to use in the context of medication nonadherence, requiring reinduction and restabilization on buprenorphine or medically supervised withdrawal from opioids and an appropriate period of abstinence before restarting naltrexone. Some patients may have sustained abstinence and choose to remain on their maintenance buprenorphine or naltrexone dose. However, others may try to taper their buprenorphine dose, discontinue naltrexone, consider a change in pharmacotherapy (e.g., from buprenorphine to naltrexone or naltrexone to buprenorphine), or attempt maintenance of remission of OUD without any medication.

Because OUD is often a chronic and relapsing illness, patients may have different types and durations of treatment over their lifetimes. Some may have periods of successful outpatient treatment at different times with all three available FDA-approved medications for OUD. Others may experience forced medication discontinuation (e.g., insurance lapse, time in controlled environments that disallow or discriminate against OUD medication, cases in family and drug courts, parole and probation). A relative few may remain in remission after successfully discontinuing medication voluntarily. Different treatment journeys occur in different treatment settings (e.g., intensive outpatient or residential programs) and with different pharmacotherapies and ancillary psychosocial and recovery support services.

To the extent possible, coordinate primary care, behavioral health, and wraparound services needed and desired by the patients to address their medical, social, and recovery needs. Individuals with co-occurring physical, mental, and substance use disorders may benefit from collaborative care.[352]

Resource Alert: Substance Abuse and Mental Health Services Administration (SAMHSA) Treatment Guidance for Individuals With Co-Occurring Disorders

- TIP 42, *Substance Abuse Treatment for Persons With Co-Occurring Disorders,* provides treatment strategies for SUD treatment for individuals with mental disorders (https://store.samhsa.gov/shin/content//SMA13-3992/SMA13-3992.pdf).
- *General Principles for the Use of Pharmacological Agents To Treat Individuals With Co-Occurring Mental and Substance Use Disorders* offers assistance for the planning, delivery, and evaluation of pharmacotherapy for individuals with co-occurring mental and substance use disorders (https://store.samhsa.gov/shin/content//SMA12-4689/SMA12-4689.pdf).
- *Pharmacologic Guidelines for Treating Individuals With Post-Traumatic Stress Disorder and Co-Occurring Opioid Use Disorders* is tailored to the provision of medication for OUD to individuals also diagnosed with posttraumatic stress disorder (https://store.samhsa.gov/shin/content//SMA12-4688/SMA12-4688.pdf).

Role of the Treatment Plan and Treatment Agreement in Medical Management

The initial treatment plan should include:

- **Treatment goals.**
- **Conditions for changing or stopping treatment** (the Chapter 3E Appendix has a sample goal-setting form).
- **Therapeutic contingencies for nonadherence and failure to meet initial goals**, such as:
  - Increase in the intensity or scope of services at the office or through referral.
  - More intensive psychosocial treatment, including inpatient treatment or transfer to an opioid treatment program (OTP) for observed buprenorphine dosing if the office-based practice is unable to provide such services.
  - Reassessment to ensure psychiatric and other comorbid addictions are adequately addressed via consultation with mental health, addiction treatment, or pain management providers as available and indicated.

Some patients may need a more structured environment when there is continued opioid use or comorbid use of substances other than opioids or when mental disorders are impeding their progress toward remission and recovery. In these cases, medication for OUD should not be interrupted.

Treatment agreements can help clarify expectations for patients and healthcare professionals (see the Chapter 3C Appendix and Chapter 3D Appendix for sample treatment agreement forms for naltrexone and buprenorphine, respectively). Review and amend treatment plans and treatment agreements periodically as patients progress (or destabilize) and new goals emerge. This will help healthcare professionals across settings deliver coordinated, effective care. Updating treatment plans and agreements helps patients recognize their progress and supports their motivation to remain engaged. Involving patients' support networks makes patients accountable to a group of caring people rather than to a single healthcare professional.

If a patient does not discontinue all illicit drugs for extended periods, it doesn't mean treatment has failed and should not result in automatic discharge. It means the treatment plan may require modification to meet the patient's needs.

Engage patients' family members and other recovery supports (with patients' written consent) by sharing their treatment goals and agreements. Identify specific ways they can support patients' goals.[353]

Medical Management Strategies

Medical management includes:

- Providing brief supportive counseling.
- Referring to ancillary psychosocial services.
- Referring to psychiatric and medical care if not directly provided by the healthcare professional prescribing or administering OUD medication.
- Adjusting the frequency of office visits.
- Conducting drug tests.
- Monitoring patient adherence to medication with occasional observed dosing, random medication inventorying, or both.

- Addressing patient concerns about side effects.
- Discussing any concerns with the patient or their support network.
- Prescribing medication for co-occurring alcohol use disorder (e.g., disulfiram, acamprosate).

Strategies for optimizing medical management and brief supportive counseling involve:

- **Helping the patient manage stressors and identify triggers** for a return to illicit opioid use.
- **Providing empathic listening and nonjudgmental discussion** of triggers that precede use or increased craving and how to manage them.
- **Providing ongoing assessment to mark progress.** Revise treatment goals via shared decision making to incorporate new insights. (See "Treatment Planning" in Part 2 of this TIP for more on shared decision making.)
- **Providing medical care for comorbid health conditions.**
- **Referring patients as needed** to:
  - Adjunctive psychiatric treatment.
  - Addiction counseling.
  - Case management.
  - Community-based recovery support groups.

The TIP expert panel recommends medication management and brief supportive counseling at each visit. Refer for adjunctive addiction counseling and other psychosocial supports as clinically indicated.

- **Inviting supportive family members and friends to medical visits** to discuss strategies to support patients.
- **Engaging and educating family members and friends** who are reluctant to accept medication's role in treatment.
- **Advocating for patients as needed** if their treatment becomes threatened by their employer, housing provider, insurance company, the courts, or criminal justice agencies. These threats, refusal of service, or frank coercion may constitute potential violations of the Americans with Disabilities Act or other discrimination or parity violations.

Referral to counseling and other psychosocial supports

Prescribers of buprenorphine must be able to refer patients for appropriate adjunctive counseling and ancillary services as needed according to federal law.[354] (However, patients can still receive buprenorphine treatment even if they do not use such services.) There's no such referral requirement for naltrexone treatment, but patients should receive medical management and be referred as needed for adjunctive addiction, mental health, or recovery services.

To achieve clinical stability and abstinence from illicit drug use, many patients need psychosocial counseling and support services beyond what their buprenorphine prescriber's practice offers. For example, patients with mental disorders (e.g., depression, posttraumatic stress disorder)[355] should be assessed and treated with appropriate medications (as indicated) and adjunctive mental health services.

Some patients are reluctant to engage in addiction counseling or recovery support groups until they stabilize on medication. Once stabilized, they may see benefits to participating in these supports. Recommend additional addiction, mental health, and social services as appropriate if patients:

- Do not achieve full remission.
- Continue to misuse nonopioid substances.
- Do not reach their treatment goals with medication management alone.

Behavioral treatment with contingency management (e.g., rewards for illicit drug abstinence) is highly effective and is offered in some specialty treatment programs. It can motivate the patient to reduce illicit drug use, including opioids and stimulants, and increase medication adherence.[356]

Alcoholics Anonymous, Narcotics Anonymous, Self-Management and Recovery Training, and other **peer recovery support groups can be helpful to patients, especially if they find groups with accepting attitudes toward OUD medication and people who take it.** (See Part 5 of this TIP for resources on recovery support groups.) Some peer recovery support groups consider patients taking methadone and buprenorphine for OUD treatment as not being abstinent from opioids. Check with local groups before referring a patient. Groups not accepting of OUD medications are not appropriate for patients taking them. Patients are most likely to benefit from peer support programs if they actively participate in offered recovery activities.[357] Monitor recovery activities to ensure that patients are accessing appropriate supports and are benefiting from them (Exhibit 3E.2)

Exhibit 3E.2. Monitoring Recovery Activities

At medical management visits, do not simply ask about attendance at recovery support meetings—explore the level of participation and engagement in those activities. Some activities include:

- Finding and working closely with a sponsor.
- "Working" the 12 Steps at 12-Step meetings and with a sponsor.
- Doing service at meetings (e.g., setting up chairs, making coffee, going on a "commitment" to speak at a meeting in a jail or an inpatient drug and alcohol program).
- Having and frequently attending a regular "home" group.[358]

Remember this statement from recovery experts A. Thomas McLellan and William White: "Recovery status is best defined by factors other than medication status. Neither medication-assisted treatment of opioid addiction nor the cessation of such treatment by itself constitutes recovery. Recovery status instead hinges on broader achievements in health and social functioning—with or without medication support."[359]

Patients may need many other psychosocial services. Case managers can help patients obtain:

- Housing support.
- Medicaid or other health insurance.
- Income support.
- Food assistance services.
- Vocational and educational services.
- Mental health and family therapy.

Refer to psychosocial services as appropriate. Get patient consent to share information and make provider introductions, just as referrals to other medical specialists would occur. Strategies include:

- Referring per program availability, affordability, and patients' needs, preferences, and treatment responses. Ensure referrals to programs that accept and support patients receiving OUD medication.
- If possible, personally introducing patients to the new behavioral health service providers or peer recovery support specialists if changing settings, to encourage a successful transition.
- Developing and maintaining a list of referral resources, including:
  - Drug and alcohol counselors.
  - Inpatient, residential, and outpatient addiction counseling programs.
  - OTPs.
  - Inpatient/outpatient behavioral health programs.

  - Primary care and mental health providers.
  - Community-based services.
  - Recovery support groups.
- Using active referral procedures (e.g., linking patients directly via phone to a specific program staff member) instead of passive ones (e.g., giving a patient a name and a phone number to call).
- Avoiding leaving patients to find their own referrals.
- Monitoring patients' follow-through via phone contact or at the next office visit.

Frequency of medical management visits

The TIP expert panel as well the American Society of Addiction Medicine (ASAM) recommend that patients be seen approximately once a week until they demonstrate significant reductions in or abstinence from illicit substance use.[360] This is also a time to ensure adherence to pharmacotherapy. Nonadherence to naltrexone or buprenorphine prevents optimal treatment outcomes. In scheduling patient visits, be sensitive to treatment barriers such as:

- Work and childcare obligations.
- Cost of care and lack of insurance coverage.
- Driving time.
- Lack of public transportation to visits, which may be particularly challenging for patients in rural areas.

Goals of weekly visits include:

- Assessing patients' clinical needs and challenges.
- Assessing medication effectiveness and side effects.
- Assessing functional status (e.g., home, work, school).
- Assessing and monitoring stress coping strategies and potential triggers for return to substance use.
- Assessing adherence to the recommended frequency of attendance for XR-NTX injections or the prescribed buprenorphine dosing regimen and responsible handling of the medication (e.g., safely storing out of reach of children, taking as prescribed, not sharing or losing it).
- Monitoring use of alcohol and illicit drugs and ensuring adequate therapeutic dosing (e.g., opioid blockade if there is ongoing illicit opioid use and adherence to medication).
- Following up on any referrals made, such as adjunctive counseling, recovery support groups, or other psychosocial services (the Chapter 3E Appendix has a sample medical management visit form).

Once patients adhere to therapeutic doses of OUD medication, decrease illicit drug and alcohol use, and increase negative opioid toxicological samples, consider less frequent visits. Monthly visits (or less for carefully selected patients who have been stable on buprenorphine for extended periods with adequate support) are reasonable for patients taking naltrexone or buprenorphine who show progress toward treatment objectives. Indications that a patient is ready to come less than weekly include:

- Several weeks of illicit opioid abstinence based on self-report and negative drug tests.
- Adherence to appointments and treatment plan.
- No ongoing drug use that may risk patient safety (e.g., alcohol or benzodiazepine misuse).
- Absence of significant medication side effects.
- Stable mental health and medical conditions.
- Responsible handling of medication (e.g., safe storage, no requests for early refills).
- Absence of unexpected controlled medication prescriptions from other providers in the PDMP.

As visits become less frequent, consider random urine drug testing, medication counts (buprenorphine tablets or films), and involvement of network supports if available.

Buprenorphine implants are indicated only for stable patients already taking transmucosal buprenorphine with positive treatment response. Extended-release buprenorphine is indicated for patients treated with transmucosal buprenorphine for at least 1 week. It's expected that patients with the implants or those treated with extended-release buprenorphine will receive medication management services with visits approximately weekly at the start and then less frequently as clinically indicated based on patient treatment response. Likewise, patients treated with XR-NTX should be seen more than once per month when initiating the medication, to monitor progress and assess and address any side effects.

Visit frequency should not depend only on dosing schedule for long-acting OUD medications. Also consider patients' treatment needs, preferences, and responses. To ensure continued engagement, consider adding to the treatment agreement the expected visit frequency and frequency of other ancillary treatments tailored to patients' needs, goals, and preferences.

Drug testing in ongoing medical management

Ongoing clinical monitoring that includes drug testing of urine or oral fluid specimens is part of good practice. Objective evidence of any ongoing illicit substance use is important to consider along with patient reports. Patients may not wish to disclose recent drug use because of shame, fear of punishment, or even fear of discharge from treatment.

Explain to patients that testing will help them meet treatment goals and is not performed to render punishments. Results help:

- Detect medication nonadherence that could cause harm (e.g., unintentional overdose).
- Monitor abstinence and response to medication treatment.
- Counsel and improve treatment plans.
- Detect a return to illicit opioid use or other substance use.

The TIP expert panel recommends periodic random testing. Drug testing frequency should be clinically determined. It should occur at least at the time of the initial evaluation and initiation of medication (naltrexone, buprenorphine) and at a frequency consistent with office visits (e.g., weekly initially).

Point-of-service tests give immediate results, allowing findings and implications to be discussed with patients during visits. However, some circumstances require confirmatory laboratory testing, such as when the patient contests the results and when testing for employment or legal monitoring. In these cases, samples may need to be collected and sent to a Department of Health and Human Services-certified laboratory under strict chain-of-custody procedure. In addition, norbuprenorphine may not be available in point-of-service tests and therefore, periodically, a specimen should be sent to a laboratory for testing. Important aspects of testing include:

- Testing technology.
- The cutoffs for positive tests.
- Any administrative requirements.
- Time windows to detect a positive result.
- Cross-reactivity, sensitivity, and specificity.
- Test interpretation. (See Part 2 for more information about how to interpret drug testing results.)
- Consideration of panels based on drugs most commonly used in the region.

Conduct point-of-service drug tests following the manufacturer's instructions. Use Clinical Laboratory Improvement Amendments-waived testing kits. A provider's office must enroll and pay a modest fee for certification. The application is available online (www.cms.gov/Medicare/CMS-Forms/CMS-Forms/downloads/cms116.pdf).

Sample collection via oral swab is straightforward; follow the manufacturer's directions. **If collecting urine samples, take steps to reduce the likelihood of tampering.** In settings that treat many patients or treat patients potentially facing criminal justice sanctions, consider taking these measures:

- Have patients visit the bathroom alone, without bags or jackets, to deter use of another person's urine specimen.
- Set the sink to run only cold water and use a colored toilet bowl cleaner to prevent dilution of urine specimens.
- Use specimen cups with specific gravity testing, if possible, to identify diluted samples.
- Use temperature-sensitive strips in collection cups to identify tampered specimens.

Ongoing positive opioid tests during treatment indicate the need to reassess the patient and revise the treatment plan. Repeated positives may indicate that patients:

- Are not taking some or all of their medication or may be taking the medication incorrectly.
- Need a different medication.
- Need directly observed medication administration in the office or at an OTP.
- Need a buprenorphine dose increase.
- Need more counseling or a higher level of a specialty addiction treatment program.
- Need to participate in recovery support services.

For more information on drug testing in the primary care setting, see Technical Assistance Publication 32, *Clinical Drug Testing in Primary Care*[361] (https://store.samhsa.gov/shin/content//SMA12-4668/SMA12-4668.pdf) and ASAM's Consensus Statement on Appropriate Use of Drug Testing in Clinical Addiction Medicine.[362]

Opioids and opiates in point-of-service tests

Point-of-service and laboratory screening tests for opiates only test for opioids metabolized to morphine (e.g., codeine, heroin). Semisynthetic and synthetic opioids, such as methadone, buprenorphine, and others (e.g., fentanyl, oxycodone), are not metabolized to morphine and do not test positive on most opiate tests. Specific point-of-service tests exist for these opioids.

Some point-of-service and laboratory tests can detect methadone, buprenorphine, and other opioids. Patients taking buprenorphine should have buprenorphine specifically included in their urine test panel to assure the prescriber that the patient is indeed taking the medication. Some patients may put some of their buprenorphine in the urine to mask nonadherence. Periodically testing for a buprenorphine metabolite (e.g., norbuprenorphine, buprenorphine glucuronide) is advised.

Assessing buprenorphine adherence

Medication nonadherence and diversion can signal inadequately treated OUD (e.g., return to use with positive urine drug tests). Assess such behaviors clinically and develop therapeutic responses to them.

Remember that nonadherence, misuse, and diversion occur with other medications as well—those with and without abuse potential. For instance, it's clear that opioid analgesics have been overprescribed for pain, misused, and diverted; they have contributed to deaths among individuals prescribed as well as

those not prescribed these medications. Antibiotics for bacterial infections are also overprescribed, and patient nonadherence (e.g., not completing the full course), misuse (e.g., saving leftover medication for a later self-diagnosed and self-treated infection), and diversion (e.g., giving leftover medication to ill family members or friends) can cause significant public health harm, given the spread of drug-resistant bacteria. **Medication nonadherence has largely fueled development of longer acting medications** (e.g., depot antipsychotics, long-acting contraceptives, XR-NTX, buprenorphine implants).

Strategies for addressing medication nonadherence and diversion include carefully assessing the patient to understand underlying causes of the behavior. Address these causes and monitor adherence. For instance, if a patient gives his or her medication to a relative on a waitlist for treatment, getting the relative into treatment can help that patient become adherent. Monitor adherence by:

- Asking patients to bring their unused medication into the office for counting.
- Increasing the frequency of office visits.
- Increasing urine drug testing.
- Talking with family members or significant others.
- Writing prescriptions for shorter duration.
- Observing medication administration at the office, pharmacy, or an OTP.
- Checking urine for buprenorphine and its metabolites.
- Checking the PDMP.
- Avoiding doses over 24 mg (save in rare cases).

Chapter 3D Appendix includes a sample patient urine drug screen and medication count form, as well as a pharmacy tablet/film count form.

If these steps have no positive effect, patients may need referral to higher levels of care at OTPs or residential addiction treatment programs. Different formulations or pharmacotherapy may need to be considered.[363] If a change in setting is required, consider patients for return to OBOT once they stabilize.

Discontinuing medication for OUD

Patients should decide whether to taper off or discontinue pharmacotherapy with the support of their healthcare professional and, if applicable, their addiction or mental health counselor, family, and peer recovery supports (e.g., peer support specialist, recovery coach). If patients' goals include stopping medication, discuss the risks and benefits of discontinuing. Work closely with patients to develop a buprenorphine dose taper plan, if needed, and a robust plan to sustain recovery and reengage in treatment before any return to substance use. Before patients begin a buprenorphine dose taper or discontinue XR-NTX, they should demonstrate:

- Medication adherence.
- Abstinence from illicit opioid use.
- A stable living environment.
- Social support.
- Sustained improvements in functioning at home and at school or work.

Consider treatment with XR-NTX following successful taper from an opioid agonist or partial agonist (after an appropriate period of abstinence). Data are limited on the effectiveness of this approach.

The TIP expert panel recommends that providers not discharge patients from treatment solely because of continued illicit opioid use if the benefits of treatment continue to outweigh the risks. If

risks outweigh benefits or alternative treatments may offer more benefit, refer patients to alternative treatment (e.g., OTP). Discharging patients without attempting meaningful referral when illicit opioid use is ongoing can worsen the patient's condition and may be considered patient abandonment.

Forced tapers or abrupt discontinuation

Forcing a patient to taper off of medication for nonmedical reasons or because of ongoing substance misuse is generally inappropriate. Many patients are abruptly discontinued or tapered from OUD medication against their will while detained or awaiting trial. A randomized trial of continuing versus tapering off methadone for detainees found that those who kept taking medication in detention were significantly more likely to return to treatment on release.[364] It's likely that the same holds true for forced discontinuation from buprenorphine during detention.

As is sometimes the case in general medical practice, **patients who are unable to pay their bills should not be discontinued from treatment without attempting meaningful referral.** Attempt referrals to publicly funded addiction treatment services (e.g., specialty treatment programs, federally qualified health centers). If patients cannot continue treatment because of inability to pay, providers can contact the pharmaceutical company about patient assistance programs to help defer the cost of medications.

Forced dose tapers against the patient's desire may be clinically indicated when risks of treatment outweigh benefits or, in unusual cases, where the patient has been violent toward staff or other patients. In these cases, attempt to place the patient in a higher level of care and document the attempt. In some circumstances, forced tapering or abrupt discontinuation may violate the Americans with Disabilities Act. The Legal Action Center (www.lac.org) and the National Alliance for Medication Assisted Recovery (www.methadone.org) offer information on how to legally manage forced tapers.

Patient follow-up

Medical management should not end when patients taper off of medication. The TIP expert panel recommends regular follow-up visits (or phone checkups by clinical staff or recovery support specialists) to help patients manage their condition, address potential concerns about returning to illicit opioid use and discuss reinitiating OUD maintenance medication if warranted. Attendance at drug counseling or mutual-help groups can be helpful, as can periodic drug testing.

Do not require discontinuation of pharmacotherapy because of incomplete treatment response. Doing so is not a rational therapeutic response to the predicted course of a chronic condition.

Administrative Considerations

Patient Limits

Physicians

After taking the necessary training, qualified physicians can obtain waivers to prescribe buprenorphine to up to 30 active patients at any one time. Such providers may apply to SAMHSA to increase their patient limit to up to 100 patients if they've had a waiver for at least 1 year. Physicians with a waiver to prescribe to up to 100 patients for at least 1 year may apply to SAMHSA to prescribe to up to 275 patients under more restrictive conditions. More information on patient limits and applying for limit increases is available from SAMHSA (www.samhsa.gov/sites/default/files/programs_campaigns/medication_assisted/understanding-patient-limit275.pdf).

Nurse practitioners and physician assistants

Qualified nurse practitioners and physician assistants can obtain waivers to prescribe buprenorphine to up to 30 patients the first year and 100 patients thereafter. These practitioners must complete 24 hours of additional training to qualify. More information is available from SAMHSA (www.samhsa.gov/medication-assisted-treatment/qualify-nps-pas-waivers).

Diversion Control Policies for OBOT With Buprenorphine

Controlled substance diversion refers to unauthorized provision of medication to someone for whom it was not prescribed.[365] **Patients may divert buprenorphine for various reasons,** such as:

- To "help" someone who needs medically supervised withdrawal or awaits treatment.[366,367]
- To provide income for the seller.
- To enable someone else to experience the euphoric effect of the medication.[368]

Address diversion of controlled substances with patients using the following strategies:

- Clarify that continuing in office-based treatment depends largely on taking medication as prescribed; nonadherence and diversion are thus problematic.
- In a nonjudgmental way, discuss to whom within their network of family, friends, and acquaintances they might be tempted to divert their medication and why they might be tempted to do so.
- **Instruct patients to store medication securely** (children may inadvertently ingest it and overdose, or other people may take the medication for their own use or to sell).[369]
  - Discuss patients' plans to safely store buprenorphine. Advise patients to keep the medication in the original packaging and out of the reach of children.[370]
  - Tell patients not to store in common areas (e.g., kitchen, bathroom) where others may access it.
  - Educate patients that any portion of a dose taken by a child or pet can be deadly and that they should call 9-1-1 immediately if this occurs.
- Explain how diversion causes negative views of treatment, leading to discrimination against people with OUD. Therefore, healthcare professionals must proactively address diversion to help prevent it.

Possible signs that a patient is diverting buprenorphine[371] include:

- Frequently missed appointments.
- Requests for early refills because medication was reportedly lost or stolen.
- Negative buprenorphine urine screens.
- Positive buprenorphine urine screens that are negative for buprenorphine metabolites.
- Specific requests for the buprenorphine monoproduct owing to naloxone allergy.
- Specific requests for doses of buprenorphine greater than 24 mg/6 mg.
- PDMP shows prescription fills for opioids or other medications that are not positive on his or her drug tests.
- Failed film/pill callback counts.

Establish a diversion control plan to minimize OUD medication diversion. The plan provides measures to reduce diversion and assigns specific responsibility to medical and administrative staff members for

carrying out these measures.[372] It should address medication storage, dispensing and administration (if applicable), and prescribing.[373] (see the Chapter 3E Appendix for a sample diversion control policy. For providers who store buprenorphine for administration and dispensing, plans should indicate how they will control diversion and which approaches they will use to ensure that patients take their medication. Exhibit 3E.3 summarizes key elements of a diversion control plan.

Physicians who prescribe buprenorphine to more than 100 patients need a diversion control plan. Document diversion incidents and responses to incidents in the patient record. More information about DEA requirements for Drug Addiction Treatment Act of 2000 (DATA 2000)-waivered healthcare professionals is available online (www.deadiversion.usdoj.gov/pubs/docs/dwp_buprenorphine.htm).

Exhibit 3E.3. Key Elements of an OBOT Clinic Diversion Control Plan[374]

New Patients	Ongoing Patients
Check the state's PDMP before admission to determine whether patients are receiving opioids or benzodiazepine prescriptions from other providers. Ask patients to sign a release of information to speak with the other prescribers. Patients who are unwilling to sign a release of information are poor candidates for outpatient treatment. Review the clinic diversion control policy with new patients. This should include counseling patients to: • Keep buprenorphine locked up and out of children's reach. • Never share medication with anyone. • Never sell medication to anyone. • Note giving/selling medication to others as illegal. • Take medication only as prescribed. • Review, understand, and agree to the practice's buprenorphine treatment agreement before they start. Prescribe buprenorphine/naloxone when possible rather than the monoproduct. Exceptions include prescribing the monoproduct for pregnant women with OUD. Prescribe an adequate but not excessive dose. Most patients respond to doses at or below 24 mg per day. Carefully evaluate requests for higher doses and confirm, document, and assess medication adherence continuously.	Periodically check the state's database. Conduct random urine tests that include a wide spectrum of opioids—including morphine, oxycodone, and buprenorphine—and periodically include buprenorphine metabolites. This will help monitor response to treatment and determine whether patients are taking at least some of their prescribed buprenorphine. Use **unobserved** specimen collection to preserve patient privacy and dignity: • Do not let patients bring backpacks, jackets, or other items into the bathroom. • Do not let others enter bathrooms with patients. • Temperature test the urine sample. Use **observed** specimen collection (obtained by a staff member of the same gender) or oral fluid testing if there is reason to suspect tampering or falsification. Contact patients at random; ask them to bring in their medication within a reasonable period (24 to 48 hours) to count the tablets/films to ensure that all medication is accounted for. Provide a limited number of days of medication per prescription without refills (e.g., several days or 1 week per prescription) until the patient has demonstrated stability and lowered diversion risk.

Storage of Buprenorphine

Practices that store buprenorphine onsite must have appropriate security, which includes storing the medication in a securely locked, substantially constructed cabinet.[375] If a significant amount of stored buprenorphine is lost or stolen, providers must notify the local DEA office in writing within 1 business day and complete a Form DEA-106 (https://apps.deadiversion.usdoj.gov/webforms/dtlLogin.jsp).

Employees convicted of a felony related to a controlled substance or who had a DEA registration denied, revoked, or surrendered "for cause" are not permitted to have access to buprenorphine.

Records for Dispensers

Office-based practices that dispense buprenorphine must keep records of:[376]

- The number of units and doses dispensed with the names and addresses of the patients.
- The dates the medication was dispensed.
- The names (or initials) of the staff members who dispensed or administered the medication.

The diversion control plan should include approaches to ensuring that patients take the medication and do not divert it to others.

Recordkeeping for ordering, storing, and dispensing buprenorphine in the office

All prescribers and staff members must follow federal and state laws for ordering, storing, administering, and dispensing buprenorphine in outpatient settings. Records of inventories of medication received, dispensed, destroyed, and lost or stolen must be maintained. For guidance on how to comply with federal requirements, see:

- Diversion Control Division's *Practitioner's Manual* (www.deadiversion.usdoj.gov/pubs/manuals/pract).
- FDA Recordkeeping Requirements for Buprenorphine Treatment (www.buppractice.com/node/12246).

Recordkeeping for prescribing buprenorphine

Consider writing an initial prescription for only a few days. An example of a 1-day in-office induction prescription is:

> *Buprenorphine/naloxone 2mg /0.5 mg: Dispense #4 for in-office induction, no refills, fill on _____ [insert date that is 1 day before the scheduled induction to make it less tempting for patients to use on their own before induction]*

Keep a log for possible DEA inspection that includes:

- Patients' names (or ID numbers).
- Dates of prescriptions.
- The names, strengths, and quantities of the medications.

Although not required, such a log facilitates inspection and indicates that the provider is within the approved patient limits. Alternatively, electronic health records can be used for this purpose.

DEA Inspections

Under DATA 2000, DEA must ensure that providers administering, dispensing, or prescribing buprenorphine are following recordkeeping, security, and other requirements. To fulfill this requirement, **DEA conducts routine, unannounced onsite inspections.** A description of the inspection process and how to comply with its requirements is available online (http://pcssmat.org/wp-content/uploads/2014/02/FINAL-How-to-Prepare-for-a-DEA-Inspection.pdf).

Emergency Protocols and Patient Safety Measures

Clinics that provide buprenorphine or naltrexone do not need special emergency protocols, crash carts, or other special equipment. However, for patient safety, **the TIP expert panel recommends having injectable or intranasal naloxone onsite.** Clinics that administer XR-NTX or buprenorphine should have a written policy and procedure for responding to precipitated withdrawal and medication allergies.

On-call services and backup during absences should be available either directly or through contracts or cooperative agreements with other local providers with waivers. Qualified medical staff can offer routine medical and psychiatric coverage even without a buprenorphine waiver.

Providers who give more than 100 patients buprenorphine must have on-call services. Such services are valuable regardless of the number of patients in treatment.

Recommendations for Staff Member Training

All staff members who interact with patients are part of the treatment environment. They can affect patients' treatment experiences and, ultimately, their outcomes. Staff members who interact with patients can include receptionists, billing clerks, urine specimen collection clerks, and all clinical staff members. Therefore, it is useful to **educate and train all staff members in key areas,** including:

- Organizational mission.
- The scientific and empirical underpinnings for the use of FDA-approved medications for OUD, how these medications work, and the evidence for their effectiveness.
- The similarity of medical management and support of patients with OUD to that of patients with other chronic illnesses.
- The importance of maintaining a nonjudgmental and welcoming attitude toward patients.
- How to hold discussions about negative perceptions and prejudices associated with OUD.
- Side effects of OUD medications and procedures to alert staff members when patients exhibit them.
- The effect of OUD and other substance use and mental disorders (including posttraumatic stress disorder) on patients' behavior and how staff members can respond appropriately.
- Procedures for seeking help from other staff members to deescalate disagreements or solve problems.
- Procedures for protecting patients' confidentiality and safety.

Treating OUD can be a challenging yet rewarding part of a clinical practice. Addressing key administrative issues keeps the focus on the rewarding aspects of developing long-term relationships with patients as they work to overcome negative effects of OUD on their lives and improve their health.

Resource Alert: Training and Mentorship for Prescribers

The Providers' Clinical Support System, with the American Academy of Addiction Psychiatry as the lead organization along with partners from the American Society of Addiction Medicine and other professional organizations, delivers education, training, and mentorship to providers who wish to treat OUD with medications. More information about training and professional mentorship is available online (http://pcssmat.org).

Chapter 3E Appendix

Sample Goal-Setting Form

Name:
Date:

Goal Category	**Current Situation Score** (10 = major problems and 0 = no problems)	**What would need to change to decrease this score?**	**Priority Score** (10 = highest priority ["I really want to work on this"] and 1 = lowest priority ["I really do not want to work on this")
Opioid use			
Other illicit drug use: _____			
Alcohol use			
Tobacco use			
Physical health			
Mental health			
Legal/court issues			
Finances			
Job/employment			
Hobbies			
Family relations			
Partner relations			
Supportive drug-free network			
Education			
Keeping medication safe (e.g., not giving it away, selling it, having it stolen)			
Other:			
Other:			

M. Lofwall, February 27, 2017 (personal communication). Adapted with permission.

Sample Buprenorphine Diversion Control Policy

XYZ Medical Practice

Office-Based Opioid Use Disorder Policy and Procedure Manual

Policy Title: Diversion Control for Patients Prescribed Transmucosal (Sublingual) Buprenorphine

Effective Date: _____ (Month, Day, Year)

This Diversion Control Policy is provided for educational and informational purposes only. It is intended to offer healthcare professionals guiding principles and policies regarding best practices in diversion control for patients who are prescribed buprenorphine. This policy is not intended to establish a legal or medical standard of care. Healthcare professionals should use their personal and professional judgment in interpreting these guidelines and applying them to the particular circumstances of their individual patients and practice arrangements. The information provided in this Policy is provided "as is" with no guarantee as to its accuracy or completeness.

Preamble: Healthcare professionals can now treat up to 275 patients with buprenorphine. This increased access may contribute to increased diversion, misuse, and related harms. Signs that a patient is misusing or diverting buprenorphine include (1) missed appointments; (2) requests for early refills because pills were lost, stolen, or other reasons; (3) urine screens negative for buprenorphine, positive for opioids; (4) claims of being allergic or intolerant to naloxone and requesting monotherapy; (5) nonhealing or fresh track marks; or (5) police reports of selling on the streets. Likewise, there are a range of reasons for diversion and misuse (e.g., diverting to family/friends with untreated opioid addiction with the intent of trying to "help" convince them to also get treatment; diverting to family/friends on a treatment waiting list; selling some or all of the medication to pay off old drug debts/purchase preferred opioid of misuse/pay for treatment in places where there are inadequate addiction treatment professionals taking private insurance or Medicaid for such reasons as inadequate reimbursement/no reimbursement/burdensome prior authorization process).

The safety and health of patients and others in the community could be at risk if misuse and diversion are not addressed proactively throughout treatment. The reputation of XYZ Medical Practice may also be put at risk.

Definitions: *Diversion* is defined as the unauthorized rerouting or misappropriation of prescription medication to someone other than for whom it was intended (including sharing or selling a prescribed medication); *misuse* includes taking medication in a manner, by route or by dose, other than prescribed.[377]

Purpose: Misuse and diversion should be defined and discussed with patients at the time of treatment entry; periodically throughout treatment, particularly when there have been returns to illicit drug use; and when suspected (e.g., incorrect buprenorphine pill/film count) or confirmed. These procedures will establish the steps to be taken to prevent, monitor, and respond to misuse and diversion of buprenorphine. The response should be therapeutic matched to the patients' needs, as untreated opioid use disorder and treatment dropout/administrative discharges may lead to increased patient morbidity and mortality and further use of diverted medications or illicit opioids associated with overdose death.

Procedures for Prevention:

- Use buprenorphine/naloxone combination products when medically indicated and cost is not an issue. Reserve the daily buprenorphine monoproducts for pregnant patients and patients who could not afford treatment if the combination product were required, who have a history of stability in treatment and low diversion risk, or who have arrangements for observed dosing. Buprenorphine monoproducts are recommended for pregnant women.
- Counsel patients on safe storage of, and nonsharing of, medications. Patients must agree to safe storage of their medication. This is even more critical if there are children in the home where the patient lives. Counsel patients about acquiring locked devices and avoiding storage in parts of the home frequented by visitors (e.g., do not recommend storage in the kitchen or common bathrooms). Proactively discuss how medication should be stored and transported when traveling to minimize risk of unintended loss.

Sample Buprenorphine Diversion Control Policy

- Counsel patients on taking medication as instructed and not sharing medication. Explicitly explain to patients the definitions of diversion and misuse, with examples. Patients are required to take medication as instructed by the healthcare professional; for example, they may not crush or inject the medication.
- Check the prescription drug monitoring program for new patients and check regularly thereafter. Prescription drug monitoring program reports can be a useful resource when there is little history available or when there is a concern based on observation. Check for prescriptions that interact with buprenorphine and for other buprenorphine prescribers.
- Prescribe a therapeutic dose that is tailored to the patient's needs. Do not routinely provide an additional supply "just in case." Question patients who say they need a significantly higher dose, particularly when they are already at 24 mg/daily of buprenorphine equivalents.
- Make sure the patient understands the practice's treatment agreement and prescription policies. The XYZ Medical Practice's treatment agreement and other documentation is clear about policies regarding number of doses in each prescription, refills, and rules on "lost" prescriptions. Review the policies in person with the patient. Offer an opportunity for questions. Patient and provider must sign the agreement. Review the policies again with the patient at subsequent appointments. See Sample Buprenorphine Treatment Agreement or Sample XR-NTX Treatment Agreement as needed.

Procedures for Monitoring:

- Request random urine tests. The presence of buprenorphine in the urine indicates that the patient has taken some portion of the prescribed dose. Absence of buprenorphine in the urine supports nonadherence. Testing for buprenorphine metabolites (which are present only if buprenorphine is metabolized) should periodically be included to minimize the possibility that buprenorphine is added directly to the urine sample. Dipstick tests can be subverted or replaced. A range of strategies can be used to minimize falsified urine collections including (1) observed collection; (2) disallowing carry-in items (e.g., purses, backpacks) in the bathroom; (3) turning off running water and coloring toilet water to eliminate the possibility of dilution; (4) monitoring the bathroom door so that only one person can go in; and (5) testing the temperature of the urine immediately after voiding.
- Schedule unannounced pill/film counts. Periodically ask patients who are at high risk at initial or subsequent appointments to bring in their medication containers for a pill/film count.
- With unannounced monitoring (both pill/film counts and urine tests), the patient is contacted and must appear within a specified time period (e.g., 24 hours) after the phone call. If the patient doesn't show, then the provider should consider this as a positive indicator of misuse or diversion.
- Directly observe ingestion. Patients take medication in front of the healthcare professional or another qualified clinician and are observed until the medication dissolves in the mouth (transmucosal [sublingual or buccal] absorption). Patients who are having difficulty adhering to their buprenorphine can have their medication provided under direct observation in the office for a designated frequency (e.g., three times/week).
- Limit medication supply. When directly observed doses in the office are not practical, short prescription time spans can be used (e.g., weekly or 3 days at a time.

Procedures To Respond to Misuse or Diversion: Misuse or diversion doesn't mean automatic discharge from the practice. However, it will require consideration of one or more of the following procedures:

- Evaluate the misuse and diversion. For instance, describe the incident of misuse (e.g., "the patient took the prescribed dose on three or more occasions by intravenous route immediately after starting treatment, stating that she believed the dose would not be adequate by sublingual route; she has just initiated treatment") or diversion ("the patient gave half of dose to his wife, who is still using heroin and was withdrawing, because he did not want her to have to buy heroin off the street; she is on a waiting list for treatment") and tailor the response to the behavior (e.g., reeducation of the patient on buprenorphine pharmacology in the first example above; assistance with treatment entry for the spouse in the second

Sample Buprenorphine Diversion Control Policy

example). Reassess the treatment plan and patient progress. Strongly consider smaller supplies of medication and supervised dosing for any patient who is taking medication intravenously or intranasally, or diverting, regardless of reason. Treatment structure may need to be increased, including more frequent appointments, supervised administration, and increased psychosocial support.

- Intensify treatment or level of care, if needed. Some patients may require an alternative treatment setting or pharmacotherapy such as methadone. The clinician will discuss these alternatives with the patient to ensure optimal patient outcome. This should be discussed at treatment onset so the patient is aware of the consequences of misuse and diversion.

Document and describe the misuse and diversion incident. Also document the clinical thinking that supports the clinical response, which should be aimed at minimizing risk of diversion and misuse and treating the patient's opioid use disorder at the level of care needed.

Policy adapted from ASAM's *Office-Based Opioid Use Disorder Policy and Procedure Manual,* which will be updated periodically; the most current version is available online (www.asam.org/docs/default-source/advocacy/sample-diversion-policy.pdf?sfvrsn=0).

Adapted with permission.[378]

Chapter 3F: Medical Management of Patients Taking OUD Medications in Hospital Settings

Patients with opioid use disorder (OUD) who present to emergency departments (EDs) or are admitted to hospitals for acute medical or psychiatric care can benefit from medication to treat OUD in the hospital setting. During acute medical illness, patients experiencing consequences of opioid use may be motivated to change.[379] Hospital-based providers can take this opportunity to initiate long-term medication maintenance.[380,381]

Unfortunately, less than one-quarter of patients with an opioid-related hospitalization are offered Food and Drug Administration-approved medication for OUD within 30 days of discharge.[382] Patients who already take OUD medication may also present to the hospital. Thus, a broad understanding of how to manage their OUD medication during hospitalization is necessary.

Chapter 3F guides the management of patients taking OUD medications in hospital settings. The audience is healthcare professionals in emergency, general medical, surgical, psychiatric, and obstetric units.

The keys to effective patient management in general hospital settings are:

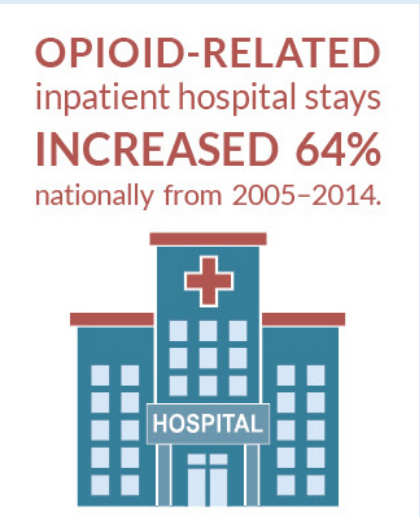
- **Balancing pharmacotherapy for OUD with other medical concerns** (e.g., surgery, pain management) during hospitalization.
- **Careful management after discharge.**
- **Seamless transfer to opioid treatment** via an opioid treatment program (OTP) or office-based opioid treatment (OBOT) provider after discharge.

Hospitalized or ED Patients Taking Medication for OUD

Buprenorphine, methadone, and naltrexone may be ordered in EDs or inpatient hospital units. It's essential for the patient to continue receiving OUD medication while hospitalized.

Pain Management

Pain management for hospitalized patients who take OUD medication is a key element of medical management. Discuss pain management and engage in a shared decision-making process with patients being treated for OUD with buprenorphine, methadone, or naltrexone. Patients may have strong preferences and opinions about pain and use of opioid analgesics for pain treatment. Some patients may want to avoid opioid analgesics. For others, inadequately treated pain may be a trigger for illicit drug use. Involve primary care pain specialists and addiction treatment providers in discussing options for managing OUD medication and pain during patient hospitalization.



Source: Weiss et al. (2017)[383]

Buprenorphine

The hospital team will need to manage buprenorphine for patients who present to the ED or are hospitalized on buprenorphine maintenance. **Physicians in inpatient settings can legally order buprenorphine without a waiver if a patient is admitted primarily for other medical reasons.**[384] Key medication management strategies include:

- **Obtaining written consent to contact the patient's providers,** including:
  - Primary care provider.
  - Buprenorphine prescriber.
  - Pharmacy.
- **Confirming the patient's outpatient buprenorphine dose** by:
  - Checking prescribing records.
  - Contacting the prescriber or pharmacy.
  - Examining recent prescription bottles.
  - Checking the prescription drug monitoring program database before administering buprenorphine.
- **Providing the usual daily dose** to the patient, once that dose is confirmed.
- Ensuring the patient's outpatient prescriber understands the reason for any missed visits.
- Informing the patient's outpatient prescriber that the patient may test positive for opioids if treated with opioid analgesics while in the hospital.
- Maintaining contact with the patient's prescriber, especially when a buprenorphine dose change is considered and in discharge planning.

Patients with pain may continue their buprenorphine while in the hospital. For mild-to-moderate pain, dividing the patient's usual buprenorphine dose three times per day (TID) may provide sufficient pain relief.[385] In some cases, increased buprenorphine dose may be appropriate. For moderate-to-severe pain, additional analgesia will be necessary. Two approaches to consider:

1. **Continue buprenorphine treatment and use full agonist opioids for added pain relief.** Because of the partial blockade caused by buprenorphine, higher-than-usual doses of opioids will probably be required for pain relief. Fentanyl, hydromorphone, and morphine have relatively high binding affinities for the mu-opioid receptor and are most likely to displace buprenorphine from receptors and provide improved analgesia. Once the painful condition has improved, if mild-to-moderate pain persists, buprenorphine can be divided TID to manage residual pain. This approach is usually successful and allows the patient to remain stable on buprenorphine.
2. **Discontinue buprenorphine upon hospitalization and use full agonist opioids to treat pain and prevent withdrawal.** This approach avoids the blockade effect of buprenorphine on the mu-opioid receptors but leaves the patient vulnerable to a return to illicit opioid use. It may be useful if the first approach does not achieve adequate pain control.[386] Consider a consult by an addiction medicine, psychiatric, or pain management provider if appropriate and available.

Pregnant women on buprenorphine can continue buprenorphine through their labor. Labor pain for pregnant patients on buprenorphine can be managed effectively with epidural analgesia or intravenous opioids. Spinal anesthesia is effective in patients on buprenorphine; patients can receive general anesthesia if needed.[387]

Perioperative pain management of patients on buprenorphine requires further study, but multiple approaches have been found effective. **Most patients can continue buprenorphine through the operative period.** Treat postoperative pain with regional anesthesia, nonopioid pain management, or full agonist opioids. Remember that higher doses are likely to be necessary. Some data suggest that buprenorphine divided TID may even be as effective as morphine for postoperative pain control.[388] Alternatively, buprenorphine can be discontinued 72 hours before a planned surgery and restarted after resolution of acute postoperative pain. The risk of this approach is that it leaves the patient vulnerable to a return to use of illicit opioids.[389]

The expert panel for this Treatment Improvement Protocol (TIP) recommends restarting buprenorphine before discharge when possible, with a proper handoff between inpatient and outpatient providers.

Methadone

The hospital team will need to manage methadone for patients who present to the ED or are hospitalized on methadone maintenance treatment. This includes pregnant women. Generally, only physicians in OTPs can order methadone to treat OUD. However, **physicians in an inpatient setting can legally order methadone administration to patients admitted primarily for other reasons.**[390]

Contact the patient's OTP directly to confirm the outpatient methadone dose, the last day of dose administration, and whether the patient was dispensed take-home doses (and how many doses) after the last dose administration at the OTP. This is to avoid double dosing and to avoid providing a full dose to a patient who hasn't been to the OTP for several days. Notify the OTP of the patient's admission and discharge so that OTP staff is aware of:

- The patient's upcoming missed visits.
- Medications received during hospitalization.
- Medications prescribed at discharge.

Clinical Caution: Do Not Rely Solely on Patient Self-Report of Methadone Dosage

Do not administer the methadone dose based on patient self-report of OTP enrollment and methadone dose; get OTP confirmation. This is important because doses above 30 mg can be lethal if the patient is not currently receiving methadone treatment and has relatively low tolerance to opioids. If it's not possible to confirm the patient's methadone dose because the OTP is closed on nights or weekends and has no emergency contact, up to 20 mg per day can be administered to treat opioid withdrawal symptoms, but monitor for signs of opioid intoxication. If the patient shows no signs of sedation or opioid intoxication 3 to 4 hours after the initial dose and continues to display symptoms of withdrawal, an additional 5 mg to 10 mg may be safe to administer.

Patients in pain should receive their full usual daily dose of methadone, barring contraindications. This is their baseline dose and should not be considered a dose for pain management. **They'll need pain medication in addition to their usual methadone dose.** If their condition is painful enough to require opioids, prescribe short-acting opioids as scheduled, not as-needed, treatment. Because these patients are already opioid tolerant, they'll likely require higher doses of opioids than patients without tolerance.[391] However, as with any patient, use nonopioid multimodal pain management when possible to minimize reliance on opioids and maximize pain control.[392]

It is important to tell patients who receive take-home doses that they should not take their own medication while in the hospital. They will receive methadone from the treatment team. Patients can be

asked to lock their take-home medications with their other valuables. It is also important to monitor these patients closely after the initial and subsequent methadone administration in the hospital. Some patients who receive take-home doses do not take their entire dose every day, so they may display signs of intoxication or frank overdose if the hospital staff gives them the full dose.

Naltrexone

Patients taking oral naltrexone for OUD treatment may continue naltrexone when admitted to the hospital if they do not have and are not at risk for developing a painful condition requiring opioid analgesia. Oral naltrexone provides full blockade of opioid receptors for up to 72 hours. Extended-release injectable naltrexone (XR-NTX) provides measurable naltrexone levels for 1 month or longer. Thus, managing acute pain in patients taking XR-NTX is complicated.

In patients who have taken naltrexone, manage severe pain intensively via nonopioid approaches, such as regional anesthesia or injected nonsteroidal anti-inflammatory drugs.

Naltrexone blockade can be overcome with very high doses of opioids, but patients must be closely monitored for respiratory depression in a setting with anesthesia services. This is especially true upon discontinuation of oral naltrexone, which dissociates from opioid receptors.

Hospitalized or ED Patients Not Taking Medication for OUD

Patients with OUD who present to the ED or are admitted to the hospital for an acute medical problem may benefit from initiating medications for OUD during their hospitalization. A thoughtful and respectful discussion of treatment options and patient-centered provision of medication can be a critical entry point into care. Research supports the efficacy of initiating either buprenorphine or methadone during acute hospital stays[393,394] and starting patients on buprenorphine in the ED.[395]

Buprenorphine Induction in the Hospital Setting

Patients admitted to the hospital for medical conditions incident to OUD can be treated with medically supervised withdrawal or maintenance with buprenorphine while on the inpatient service.[396] It is important to adequately address opioid withdrawal because hospital patients may otherwise sign out against medical advice or use illicit opioids in the hospital. **Buprenorphine can also be initiated for maintenance treatment** if there is a system in place that allows smooth and reliable discharge to an outpatient buprenorphine prescriber. Unlike methadone, a several-day delay between discharge and the first visit to the outpatient provider is acceptable for stable patients, as long as sufficient medication is provided until the patient begins outpatient treatment. The prescription for medication to be taken outside the hospital must be written by a prescriber with a buprenorphine waiver. If there is no prescriber with a waiver, it is possible to have a patient return to the hospital ED or a clinic within the hospital to have the buprenorphine dose administered by a physician (who does not need to be waivered) for up to 3 days.

To provide continuity of care at discharge, use these strategies:

- **Develop and maintain a network of local buprenorphine prescribers and other drug treatment providers.**
- **Discharge patients directly to a specific outpatient prescriber** for stabilization and maintenance after inpatient buprenorphine induction.

- **Send discharge information directly to the outpatient prescriber,** including treatment course, medications administered, and medications prescribed.

To initiate buprenorphine during hospitalization:

- Confirm that there are no contraindications to buprenorphine before initiation.
- Discontinue opioids for pain management only when no longer needed and the patient is stable enough to tolerate withdrawal.
- Wait for patients to develop opioid withdrawal symptoms.
- Initiate buprenorphine treatment.
- Individualize buprenorphine dosing.
- Follow the dosing guidance found in Chapter 3D of this TIP.

A clinical trial found that starting buprenorphine in the ED to treat OUD was more effective in linking patients to buprenorphine treatment in the community than were two other approaches without medication.[397] When patients presented in opioid withdrawal, they received 8 mg of buprenorphine in the ED. Patients who were not in withdrawal received a detailed self-medication guide and were provided buprenorphine for an unobserved home induction. In both cases, patients were given sufficient buprenorphine to take 16 mg per day at home until they could see an outpatient prescriber within 72 hours. Close follow-up with an outpatient buprenorphine prescriber was critical for dose stabilization and ongoing medication management.

Resource Alert: Telehealth Tools for the Treatment of OUD

The Substance Abuse and Mental Health Services Administration and other federal agencies have developed numerous resources to guide healthcare professionals in their use of telehealth and telemedicine approaches for OUD. These resources include information on:

- Guidance on the use of telemedicine in OTPs (https://store.samhsa.gov/shin/content/PEP15-FEDGUIDEOTP/PEP15-FEDGUIDEOTP.pdf).
- The policies that must be put in place (to comply with the Controlled Substances Act) by physicians who wish to use telehealth in treating patients with buprenorphine for OUD under the Drug Addiction Treatment Act of 2000. Federal (and sometimes state) restrictions apply, which can be reviewed by accessing 21 USC § 802 (www.gpo.gov/fdsys/pkg/USCODE-2011-title21/pdf/USCODE-2011-title21-chap13-subchapI-partA-sec802.pdf).
- Centers for Medicare and Medicaid guidance on telehealth (www.cms.gov/Medicare/Medicare-General-Information/Telehealth/index.html).
- Challenges and opportunities in using telehealth for rural populations (https://store.samhsa.gov/shin/content/SMA16-4989/SMA16-4989.pdf).
- How certified community behavioral health clinics can use telehealth approaches to expand their services (www.samhsa.gov/section-223/care-coordination/telehealth-telemedicine).

Methadone Induction in the Hospital Setting

Offer to treat hospitalized patients in opioid withdrawal with methadone (or buprenorphine) maintenance if they can continue the medication in an OTP seamlessly after discharge. Do not start patients on methadone maintenance in the hospital without a clear follow-up plan. Form relationships with local OTPs that allow discharging of patients directly into methadone maintenance treatment.

Inpatient methadone inductions should follow the same "start low, go slow" principles that outpatient inductions do (see Chapter 3B of this TIP). The initial dose should be from 10 mg to 20 mg

per day. Increase slowly by 5 mg every few days in response to symptoms of opioid withdrawal and level of sedation at the peak plasma level 2 to 4 hours after dosing.

Naltrexone Induction in the Hospital Setting

Consider XR-NTX initiation for patients who complete withdrawal in the hospital and are opioid free for 7 days (short acting) and up to 14 days (long acting). Only do so if:

- There are no contraindications (such as the need for opioid analgesia).
- The patient prefers it after a risk/benefit discussion that covers alternative treatments.
- There are available follow-up opportunities for ongoing medication maintenance upon discharge.

The TIP expert panel urges providers not to force patients to withdraw from opioid agonist treatment in the hospital, especially if they have acute illness, pain, or a mental illness.

No published data indicate this approach's effectiveness.

If a patient desires and gives informed consent for medically supervised withdrawal and naltrexone initiation while in the hospital, a first dose of naltrexone can be given before discharge. As with other medications for OUD, discharge coordination is critical. Hospitals that develop naltrexone induction protocols need to have a clear discharge plan in place for patients who will then need to continue naltrexone in the outpatient setting. Patients should be advised about the risk of overdose if return to opioid use occurs after discontinuing naltrexone.

Medical Management Plan

The key to effective treatment is to **involve patients and all treating healthcare professionals in developing a comprehensive plan for managing treatment with OUD medication during and after hospitalization.** This plan should include:

- Strategies for pain management (if required).
- In-hospital dosing procedures.
- Postdischarge coordination of care with outpatient programs and outpatient providers.

This plan ensures effective pain relief as well as continuity of ongoing care for patients taking medication for OUD.[398]

Notes

[1] Weiss, A. J., Elixhauser, A., Barrett, M. L., Steiner, C. A., Bailey, M. K., & O'Malley, L. (2017, January). *Opioid-related inpatient stays and emergency department visits by state, 2009–2014.* HCUP Statistical Brief No. 219. Rockville, MD: Agency for Healthcare Research and Quality.

[2] Department of Health and Human Services. (2016). *The opioid epidemic: By the numbers.* Washington, DC: Department of Health and Human Services.

[3] Center for Behavioral Health Statistics and Quality. (2017). *Key substance use and mental health indicators in the United States: Results from the 2016 National Survey on Drug Use and Health.* Rockville, MD: Substance Abuse and Mental Health Services Administration.

[4] American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). Arlington, VA: American Psychiatric Publishing.

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