TIP 63

MEDICATIONS FOR OPIOID USE DISORDER

Part 3: Pharmacotherapy for Opioid Use Disorder

For Healthcare Professionals

Part 3 of this **Treatment Improvement Protocol (TIP)** describes general principles of opioid use disorder (OUD) pharmacotherapy and discusses medication formulations, indications, and dosing for the three medications used to treat OUD—methadone, naltrexone, and buprenorphine.

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KEY MESSAGES

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

DEPARTMENT OF HEALTH & HUMAN SERVICES · USA

SAMHSA
Substance Abuse and Mental Health Services Administration

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Pharmacotherapy for Opioid Use Disorder

Part 3 of this TIP describes general principles of OUD pharmacotherapy and discusses medication formulations, indications, and dosing for the three Food and Drug Administration (FDA)-approved medications used to treat OUD—methadone, naltrexone, and buprenorphine. Part 3 also discusses patient management and monitoring in outpatient settings other than opioid treatment programs (OTPs) as well as medical management of patients with OUD in hospital settings.

Scope of the Problem

The United States is experiencing an opioid addiction epidemic.[1] In 2018, an estimated 2.0 million people aged 12 or older had OUD in the United States.[2] Illicit opioid use contributes to the development of OUD, the spread of HIV and hepatitis infections, and increasing numbers of overdose deaths.

OUD is a set of cognitive, behavioral, and physiological symptoms marked by an inability to stop opioid use despite negative consequences.[3] When severe, it can present as a chronic, recurring condition with compulsive opioid use that is often termed "addiction." It can cause serious physical and mental health, employment, legal, and family problems.

Each FDA-approved medication used to treat OUD can help patients achieve remission and begin or maintain recovery. Pharmacotherapy for OUD should be accompanied by individually tailored medical management and psychosocial and recovery support services as needed and wanted by patients to support their remission and recovery.

OPIOID-RELATED **EMERGENCY DEPARTMENT** visits more than doubled from 2005 to 2016.[4,5]

Medication supports the efforts of the individual to achieve lasting recovery.

Exhibit 3.1 defines key terms in Part 3. For more definitions, see the glossary in Part 5 of this TIP.

NOTE TO HEALTHCARE PROFESSIONALS

This TIP cannot replace sound clinical judgment and shared decision making based on careful patient assessment. Providers should familiarize themselves with FDA labeling of all OUD medications and current practices standards described here and in other resources such as the Providers' Clinical Support System (https://pcssnow.org/resources/resource-category/clinical-resources/).

EXHIBIT 3.1. Key Terms

Addiction: As defined by the American Society of Addiction Medicine,[6] "a primary, chronic disease of brain reward, motivation, memory, and related circuitry." It is characterized by inability to consistently abstain, impairment in behavioral control, craving, diminished recognition of significant problems with one's behaviors and interpersonal relationships, and a dysfunctional emotional response. Like other chronic diseases, addiction often involves cycles of **relapse** and **remission.** The *Diagnostic and Statistical Manual of Mental Disorders,* Fifth Edition,[7] does not use the term for diagnostic purposes, but it commonly describes the more severe forms of OUD.

Induction: Process of initial dosing with medication for OUD treatment until the patient reaches a state of stability; also called initiation.

Maintenance treatment: Providing medications to achieve and sustain clinical remission of signs and symptoms of OUD and support the individual process of recovery without a specific endpoint (as is the typical standard of care in medical and psychiatric treatment of other chronic illnesses).

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

Medical management: Process whereby healthcare professionals provide medication, basic brief supportive counseling, monitoring of drug use and medication adherence, and referrals, when necessary, to addiction counseling and other services to address the patient's medical, mental health, comorbid addiction, and psychosocial needs.

Office-based opioid treatment: Providing medication for OUD in outpatient settings other than certified OTPs.

Opioid treatment program (OTP): An accredited treatment program with Substance Abuse and Mental Health Services Administration certification and Drug Enforcement Administration registration to administer and dispense opioid agonist medications that are approved by FDA to treat opioid addiction. Currently, these include methadone and buprenorphine products. Other pharmacotherapies, such as naltrexone, may be provided but are not subject to these regulations. OTPs must provide adequate medical, counseling, vocational, educational, and other assessment and treatment services either onsite or by referral to an outside agency or practitioner through a formal agreement.[8]

Key Terms Related to OUD Medication Pharmacology

Abuse liability: The likelihood that a medication with central nervous system activity will cause desirable psychological effects, such as euphoria or mood changes, that promote the medication's misuse.

Bioavailability: Proportion of medication administered that reaches the bloodstream.

Cross-tolerance: Potential for people tolerant to one opioid (e.g., heroin) to be tolerant to another (e.g., methadone).

Dissociation: Rate at which a drug uncouples from the receptor. A drug with a longer dissociation rate will have a longer duration of action than a drug with a shorter dissociation rate.

Half-life: Rate of removal of a drug from the body. One half-life removes 50 percent from the plasma. After a drug is stopped, it takes five half-lives to remove about 95 percent from the plasma. If a drug is continued at the same dose, its plasma level will continue to rise until it reaches steady-state concentrations after about five half-lives.

EXHIBIT 3.1. Key Terms (continued)

Intrinsic activity: The degree of receptor activation attributable to drug binding. **Full agonist, partial agonist,** and **antagonist** are terms that describe the intrinsic activity of a drug.

Opiates: A subclass of opioids derived from opium (e.g., morphine, codeine, thebaine).

Opioid blockade: Blunting or blocking of the euphoric effects of an opioid through opioid receptor occupancy by an opioid agonist (e.g., methadone, buprenorphine) or antagonist (e.g., naltrexone).

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

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

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

Receptor affinity: Strength of the bond between a medication and its receptor. A medication with high mu-opioid receptor affinity requires lower concentrations to occupy the same number of mu-opioid receptors as a drug with lower mu-opioid receptor affinity. Drugs with high mu-opioid receptor affinity may displace drugs with lower affinity.

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Chapter 3A: Overview of Pharmacotherapy for Opioid Use Disorder

***Chapter 3A describes** general principles of OUD pharmacotherapy and summarizes formulations, indications, and dosing for the three FDA-approved OUD medications.*

There are three FDA-approved medications used to treat OUD, including the mu-opioid receptor partial agonist buprenorphine, the mu-opioid receptor full agonist methadone, and the mu-opioid receptor antagonist naltrexone. Extended-release naltrexone (XR-NTX) is FDA approved to prevent relapse in patients who have remained opioid abstinent for sufficient time.

Discussing medications that can treat OUD with patients who have this disorder is the clinical standard of care and should cover at least:

- The proven effectiveness of methadone, naltrexone, and buprenorphine compared with placebo and with outpatient counseling without medication.
- Risks and benefits of pharmacotherapy with all three types of medication, treatment without medication, and no treatment.
- Safety and effectiveness of the medications when used appropriately.
- Pharmacologic properties, routes of administration, and where and how to access treatment with each medication (Exhibit 3A.1).

EXHIBIT 3A.1. OUD Medications: An Overview[9,10]

CATEGORY	BUPRENORPHINE*		METHADONE	XR-NTX**
	TRANSMUCOSAL	DEPOT		
Appropriate patients	Typically for patients with OUD who are physiologically dependent on opioids.	Typically for patients for whom diversion or safe medication storage are concerns or for patients who must travel large distances to the prescriber.	Typically for patients with OUD who are physiologically dependent on opioids and who meet federal criteria for OTP admission.	Typically for patients with OUD who have abstained from short-acting opioids for at least 7–10 days and long-acting opioids for at least 10–14 days.
Pharmacology	**Opioid receptor partial agonist** Reduces opioid withdrawal and craving; blunts or blocks euphoric effects of self-administered illicit opioids through cross-tolerance and opioid receptor occupancy.	**Opioid receptor partial agonist** Reduces opioid withdrawal and craving; blunts or blocks euphoric effects of self-administered illicit opioids through cross-tolerance and opioid receptor occupancy. Note: Patients receiving a depot formulation of buprenorphine must be inducted onto buprenorphine using a transmucosal product.	**Opioid receptor agonist** Reduces opioid withdrawal and craving; blunts or blocks euphoric effects of self-administered illicit opioids through cross-tolerance and opioid receptor occupancy.	**Opioid receptor antagonist** Blocks euphoric effects of self-administered illicit opioids through opioid receptor occupancy. Causes no opioid effects.
Patient education	Tell patients: • That they will need to be in opioid withdrawal to receive their first dose to avoid buprenorphine-precipitated opioid withdrawal. • About the risk of overdose with concurrent benzodiazepine or alcohol use, with injecting buprenorphine, and after stopping the medication.	Tell patients: • For implantable rods (Probuphine®), they will need to be stable on no more than 8 mg of transmucosal Suboxone or generic equivalents. • For subcutaneous injection (Sublocade®), they must first be on a transmucosal form of buprenorphine for at least 7 days at a dose equivalent to 8 to 24 mg of buprenorphine.	Tell patients: • That their dose will start low and build up slowly to avoid oversedation; it takes several days for a given dose to have its full effect. • About overdose risk in the first 2 weeks of treatment, especially with concurrent benzodiazepine or alcohol use, and after stopping the medication.	Tell patients: • That they will need to be opioid free for at least 7–10 days for short-acting opioids and at least 10–14 days for long-acting opioids before their first dose to avoid XR-NTX-precipitated opioid withdrawal (which may require hospitalization). • About the risk of overdose after stopping the medication.

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EXHIBIT 3A.1. OUD Medications: An Overview (continued)

CATEGORY	BUPRENORPHINE*		METHADONE	XR-NTX**
	TRANSMUCOSAL	DEPOT		
Administration	Daily (or off-label less-than-daily dosing regimens) administration of sublingual or buccal tablet or film. Subdermal implants every 6 months, for up to 1 year, for stable patients. Monthly subcutaneous injection of extended-release formulation in abdominal region for patients treated with transmucosal buprenorphine for at least 1 week.	**Subdermal implants every 6 months, for up to 1 year, for stable patients.** **Monthly subcutaneous injection of extended-release formulation in abdominal region for patients treated with transmucosal buprenorphine for at least 1 week.**	Daily oral administration as liquid concentrate, tablet, or oral solution from dispersible tablet or powder (unless patients can take some home).	Every 4 weeks or once-per-month intramuscular injection.
Prescribing	Physicians, nurse practitioners (NPs), and physician assistants (PAs) need a waiver to prescribe. Until October 1, 2023, qualified clinical nurse specialists, certified registered nurse anesthetists, and certified nurse midwives also can obtain a waiver to prescribe. Any pharmacy can fill a prescription for sublingual or buccal formulations. OTPs can administer/dispense by OTP physician order without a waiver.	Prescribers must have a waiver (as for transmucosal buprenorphine) and complete the product's REMS program. Providers of the implantable rods must complete additional training in their insertion and removal. Both the implantable rods and subdermal injections are available via restricted distribution programs and are not available in retail pharmacies. OTPs can be providers of depot formulations of buprenorphine, provided the above criteria are satisfied.	SAMHSA-certified OTPs can provide methadone for daily onsite administration or at-home self-administration for stable patients.	Physicians, NPs, PAs, and, until October 1, 2023, clinical nurse specialists, certified registered nurse anesthetists, and certified nurse midwives can prescribe or order administration by qualified healthcare professionals.

*Long-acting buprenorphine implants (every 6 months) for patients on a stable dose of buprenorphine are also available through implanters and prescribers with additional training and certification through the Probuphine Risk Evaluation and Mitigation Strategy (REMS) Program. Extended-release buprenorphine monthly subcutaneous injections are available only through prescribers and pharmacies registered with the Sublocade REMS Program.

**Naltrexone hydrochloride tablets (50 mg each) are also available for daily oral dosing but have not been shown to be more effective than treatment without medication or placebo because of poor patient adherence.

Introduction to Medications That Address OUD

Methadone

Methadone is the most used and most studied OUD medication in the world.[11,12] The World Health Organization (WHO) considers it an essential medication.[13] Many clinical trials and meta-analyses have shown that **it effectively reduces illicit opioid use, treats OUD, and retains patients in treatment** better than placebo or no medication.[14,15,16] (Part 1 of this Treatment Improvement Protocol [TIP] further covers methadone's efficacy.)

In the United States, roughly 1,500 federally certified opioid treatment programs (OTPs) offer methadone for OUD. Increasingly, they also offer buprenorphine, and some provide XR-NTX. Core OTP services include medical oversight of treatment, direct observation of dose administration, take-home dose dispensing under certain conditions, counseling, and drug testing.

Some OTPs provide other services, including mental health and primary care, HIV and hepatitis C virus care, and recovery support. Even so, significant demand remains for better integration and coordination of care among OTPs, primary care services, and mental health services to treat the range of needs common in people with OUD.[17] Coordination is especially important for people with co-occurring medical, mental, and substance use disorders, who need multiple services and face challenges in treatment access and adherence.

> Although only OTPs can administer or dispense methadone for OUD, **all healthcare professionals and addiction and mental health counselors should be familiar with methadone.** Their patients may be enrolled in or need referral to OTPs.

RESOURCE ALERT

Substance Abuse and Mental Health Services Administration (SAMHSA) Federal Guidelines for OTPs

Federal Guidelines for Opioid Treatment Programs offers guidance on how to satisfy federal OTP regulations (https://store.samhsa.gov/product/Federal-Guidelines-for-Opioid-Treatment-Programs/PEP15-FEDGUIDEOTP).

Naltrexone

XR-NTX has demonstrated efficacy in reducing return to illicit opioid use, increasing treatment retention, and reducing opioid craving compared with placebo or no medication in randomized controlled trials.[18,19,20] (See Part 1 for more information on naltrexone's efficacy in OUD treatment.) Because the injectable form was approved more recently by FDA than methadone and buprenorphine, XR-NTX has been less studied than those medications. Physicians, NPs, and, PAs, and, until October 1, 2023, clinical nurse specialists, certified registered nurse anesthetists, and certified nurse midwives may prescribe or order XR-NTX for administration by qualified staff members without additional waiver requirements.

XR-NTX initiated prior to release from controlled environments (e.g., jails, prisons, residential rehabilitation programs) **may be useful in preventing return to opioid use after release.**[21] These settings are typically associated with extended periods of opioid abstinence, so maintaining abstinence for sufficient time to start naltrexone is less challenging than initiating it among outpatients in the community. Short-term pilot studies show that offering naltrexone under these circumstances can increase treatment engagement after release.[22,23]

The oral formulation of naltrexone is not widely used to treat OUD because of low rates of patient acceptance and high rates of

RESOURCE ALERT

SAMHSA Brief Guide on the Use of XR-NTX

SAMHSA's *Clinical Use of Extended-Release Injectable Naltrexone in the Treatment of Opioid Use Disorder: A Brief Guide* offers guidance on the use of XR-NTX and is available online (https://store.samhsa.gov/product/Clinical-Use-of-Extended-Release-Injectable-Naltrexone-in-the-Treatment-of-Opioid-Use-Disorder-A-Brief-Guide/SMA14-4892R).

nonadherence leading to a lack of efficacy.[24] However, consideration should be given to its use in situations where adherence can be ensured, such as with observed daily dosing. Naltrexone is also FDA approved for the treatment of alcohol use disorder and therefore may be useful for patients with both OUD and alcohol use disorder.

Buprenorphine

Buprenorphine is effective in retaining patients in treatment and reducing illicit opioid use, as demonstrated by many clinical trials comparing buprenorphine with placebo or no medication.[25] Buprenorphine treatment is available throughout the world. WHO includes it in its list of essential medicines.[26] (See Part 1 for more information on buprenorphine's efficacy in OUD treatment.)

Buprenorphine is a partial agonist with a ceiling effect on opioid activity. Hence, it is less likely than methadone and other full agonists to cause respiratory depression in an accidental overdose. This property contributed to the decision permitting buprenorphine to be prescribed to treat opioid dependence outside OTPs.[27] That being said, lethal overdose with buprenorphine is possible in opioid-naïve individuals or when it is taken in combination with central nervous system depressants such as benzodiazepines or alcohol.

Transmucosal buprenorphine is available by prescription through pharmacies, because the Drug Addiction Treatment Act of 2000 (DATA 2000) created an exception to the Controlled Substances Act to permit FDA schedule III, IV, and V medications approved to treat opioid dependence to be prescribed for that purpose outside OTPs. Buprenorphine, in various formulations, is the only medication to which DATA 2000 currently applies.

Qualifying physicians, NPs, and PAs can prescribe buprenorphine if they receive special training, obtain a SAMHSA waiver under DATA 2000, and get a unique Drug Enforcement Administration registration number. Until October 1, 2023, clinical nurse specialists, certified registered nurse anesthetists, and certified nurse midwives also are waiver-eligible to prescribe buprenorphine. This has greatly increased the number and type of settings where medication for OUD is available and the number of patients in treatment. New settings include non-OTP outpatient addiction treatment programs, as well as general medical and mental health practices or clinics (office-based opioid treatment). OTPs can also provide buprenorphine.

In 2016, FDA approved buprenorphine implants (Probuphine) that last about 6 months for patients stabilized on sublingual or buccal formulations. Implants have been found to be more effective than placebo in reducing illicit opioid use among opioid-dependent patients receiving counseling.[28] Implants are available in the same settings as other buprenorphine formulations but require waivered providers to receive specific training from the manufacturer on insertion and removal per the FDA-approved REMS (www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=IndvRemsDetails.page&REMS=356).

> **DATA 2000 restrictions currently apply only to buprenorphine used to treat OUD. They do not apply to pain treatment using buprenorphine formulations approved to treat pain.**

RESOURCE ALERT

How To Obtain a Waiver To Prescribe Buprenorphine

- Learn how to qualify for a DATA 2000 physician waiver: https://www.samhsa.gov/medication-assisted-treatment/training-materials-resources/apply-for-practitioner-waiver
- Learn how to qualify for an NP, PA, clinical nurse specialist, certified registered nurse anesthetist, or certified nurse midwife waiver: https://www.samhsa.gov/medication-assisted-treatment/training-materials-resources/apply-for-practitioner-waiver
- Learn how waivered practitioners can increase their patient limit from 30 to 100, and then to 275 patients: https://www.samhsa.gov/medication-assisted-treatment/training-materials-resources/apply-for-practitioner-waiver

In 2017, FDA approved a monthly extended-release buprenorphine injectable formulation (Sublocade) for patients with moderate-to-severe OUD who had been initiated and treated with transmucosal buprenorphine for at least 7 days. The medication is for subcutaneous abdominal injection by a healthcare provider and is intended to be available for ordering and dispensing (not by prescription to patients) in healthcare settings that receive special certification, pursuant to the FDA-approved REMS (www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=IndvRemsDetails.page&REMS=376).

Choosing an OUD Medication

Currently, no empirical data indicate which patients will respond better to which OUD medications. All patients considering treatment should be educated about the effectiveness, risks, and benefits of each of the three OUD medications, treatment without medication, and no treatment. Emphasize that OUD medications are safe and effective when used appropriately, and point out that these medications can help patients reduce or stop illicit opioid use and improve their health and functioning.

Tailor decisions to patients' medical, psychiatric, and substance use histories; to their preferences; and to treatment availability when deciding which medication and treatment to provide. Consider:

- Patients' prior response to a medication.
- The medication's side effect profile.
- The strength of the published data on safety and effectiveness.
- Patients' use of other substances (e.g., naltrexone is also approved for the treatment of alcohol dependence).
- Patients' occupation. For patients in safety-sensitive occupations, consider naltrexone.
- Patients' pregnancy status.*
- Patients' physical dependence on opioids. Patients not currently physically dependent on opioids who are returning to the community from a residential treatment program or incarceration should have the option of XR-NTX,[29] methadone, or buprenorphine based on which best suits their needs and circumstances (see below for special safety dosing considerations for methadone and buprenorphine in nontolerant patients).[30,31,32,33]

*Methadone or buprenorphine maintenance is recommended for OUD treatment during pregnancy,[34] as these medications have better maternal and infant outcomes than no treatment or medically supervised withdrawal.[35,36,37] Methadone and buprenorphine are not associated with birth defects and have minimal long-term neurodevelopmental impact on infants.[38] However, neonatal abstinence syndrome can occur, which requires hospitalization.[39] The American College of Obstetricians and Gynecologists notes that limited data exist on the safety and effectiveness of naltrexone in pregnancy.[40] Starting naltrexone rather than opioid agonist treatment in pregnancy is not recommended, given the risk of precipitated withdrawal. An expert panel did not agree on whether women already receiving treatment with naltrexone at the onset of pregnancy should remain on that medication during pregnancy.[41] Patients who were taking naltrexone before their pregnancy should weigh with their providers the risks regarding unknown potential harm to the developing fetus versus the potential benefits of continuing this medication during pregnancy.[42] Pregnant patients who discontinue naltrexone and return to opioid use should be considered for methadone or buprenorphine treatment.[43]

- Patients' preferences. Respect patients' preferences for agonist versus antagonist medication. (See Part 2 of this TIP for an indepth discussion of treatment planning.)

Comparative Effectiveness

A Cochrane review of 5 randomized clinical trials with 788 participants found that, when provided at flexible doses on an outpatient basis, methadone retained patients in treatment longer than buprenorphine.[44] That same review found that methadone and buprenorphine equally reduced illicit opioid use based on 8 studies with urine drug testing data from 1,027 participants and 4 studies with self-reported drug use from 501 participants.

There is not yet a Cochrane review on the comparative effectiveness of XR-NTX and buprenorphine. However, in 2017, two randomized trials comparing buprenorphine to XR-NTX were published. A multisite study with 570 participants in the United States compared initiating buprenorphine versus XR-NTX at 8 inpatient treatment programs.[45] That study found that patients randomly assigned to start buprenorphine had significantly lower return-to-use rates during 24 weeks of outpatient treatment compared with those patients assigned to start XR-NTX. This finding was due to the known difficulty in successfully completing induction in the XR-NTX group. However, comparing only the subgroups of those participants who did start their assigned medication, there were no significant between-group differences in return-to-use rates. In a 12-week trial in Norway with 159 participants who were opioid abstinent at the time of random assignment, XR-NTX was found to be noninferior to buprenorphine in terms of treatment retention and illicit opioid use.[46] There is no extant literature evaluating the comparative effectiveness of methadone, XR-NTX, buprenorphine implant, or extended-release buprenorphine injection to one another.

Duration of Medication

Continued treatment with buprenorphine or methadone is associated with better outcomes than medically supervised withdrawal.[47,48,49] Continued treatment with XR-NTX is associated with better outcomes than discontinuing XR-NTX.[50] Patients should be informed of the risks and benefits of discontinuing medication. Buprenorphine or methadone can be used for medically supervised withdrawal over a period of days to weeks (Exhibit 3A.2) for patients who prefer it to ongoing opioid agonist treatment. When opioid agonist medications are unavailable, the alpha$_2$-adrenergic agonist clonidine can relieve some withdrawal symptoms, although clinical trials found it less effective.[51] Pair medically supervised withdrawal with the chance to begin XR-NTX. Discontinuing medication increases risk of return to substance use and overdose death.[52] Stable patients can continue on their selected OUD medication indefinitely as long as it is beneficial.[53,54,55,56]

The TIP expert panel recommends offering maintenance therapy with medication, not short-term medically supervised withdrawal. The TIP expert panel also supports maintaining patients on OUD medication for years, decades, and even a lifetime if patients are benefiting.

During medically supervised withdrawal, ancillary medications can treat some of the withdrawal symptoms (Exhibit 3A.3).

Principles of OUD Pharmacotherapy

Basic Function

Several factors underlie the development of addiction involving opioids and the difficulty people have in achieving and maintaining abstinence from them. These factors include:[57,58]

- Short-term direct and indirect mu-opioid receptor agonist effects.
- Neuroplastic changes in the brain.
- Genetic, developmental, and environmental factors (e.g., exposure to high-risk environments, effect of stress on the hypothalamic–pituitary–adrenal axis).

EXHIBIT 3A.2. Medically Supervised Withdrawal Using Buprenorphine or Methadone

Medically supervised withdrawal using buprenorphine or methadone is appropriate when patients:

- Prefer it to treatment without medications, after they have been told the risks and benefits of this approach compared with treatment with medications.
- Wish to start XR-NTX, which is also FDA approved for the treatment of alcohol dependence.
- Are entering a controlled environment or workplace that disallows opioid agonists.

Data conflict on the ideal duration of medically supervised withdrawal.[59,60,61] Even so, shorter term dose reductions alone (formerly, "detoxification") are rarely effective.[62,63,64]

The TIP expert panel does not recommend short-term medically supervised withdrawal alone because of its high rates of return to illicit opioid use.[65,66,67] If patients prefer this approach, it should be provided with psychosocial treatment.[68] XR-NTX treatment should always be considered to reduce the likelihood of return to use after medically supervised withdrawal is completed and an adequate period of abstinence achieved,[69] as well as to reduce the likelihood of overdose death upon a return to opioid use.

If withdrawal is appropriate for the patient, the TIP expert panel recommends the following strategies:

- Individualize supervised withdrawal duration per patient preference and response to lower medication doses.
- Note that patients may benefit from nonopioid medication (e.g., clonidine, ondansetron, loperamide) or nonsteroidal anti-inflammatory medications to manage withdrawal symptoms near the end of the taper.
- Consider discontinuing dose reduction and increasing the dose if the patient begins to use illicit opioids.
- Encourage patients to continue receiving counseling, monitoring, and other psychosocial support after medication discontinuation.
- Urge patients to reenter treatment promptly if they return or think they may return to illicit opioid use.

EXHIBIT 3A.3. Medications for Management of Opioid Withdrawal Symptoms

SYMPTOM	MEDICATION
Nausea	Ondansetron, metoclopramide (avoid promethazine; it potentiates opioids)
Diarrhea	Loperamide
Anxiety, irritability, sweating	Clonidine
Insomnia	Diphenhydramine, trazodone
Pain	Nonsteroidal anti-inflammatory drugs

Methadone, buprenorphine, and naltrexone bind to the mu-opioid receptors in the central and peripheral nervous systems, gastrointestinal tract, and vascular system. In the brain, these receptors mediate opioids' analgesic and other effects (e.g., euphoria, respiratory depression, meiosis).[70,71,72] Through modulation of mu-opioid receptor activity in the brain, these medications exert therapeutic efficacy in treating OUD.

Intrinsic Activity

Intrinsic activity at the mu-opioid receptor varies based on whether the medication is a full agonist, partial agonist, or antagonist (Exhibit 3A.4). The amount of intrinsic activity corresponds to the amount of opioid receptor agonist effects. **A full agonist exerts maximal effects at increasing doses. A partial agonist has a ceiling effect.** Its opioid effects increase as the dose increases, but only up to a certain point. **An antagonist binds to the opioid receptor but does not stimulate the receptor at all.** Thus, it has no intrinsic activity regardless of its dose.

Overview of Medication Indications and Dosing

Healthcare professionals should consider pharmacotherapy for all patients with OUD. Prescribers must read FDA labels (i.e., package inserts) for the medications they prescribe. They must also evaluate patients clinically to determine the safety and effectiveness of the medication and dose.

EXHIBIT 3A.4. Intrinsic Activity of OUD Medications[73]

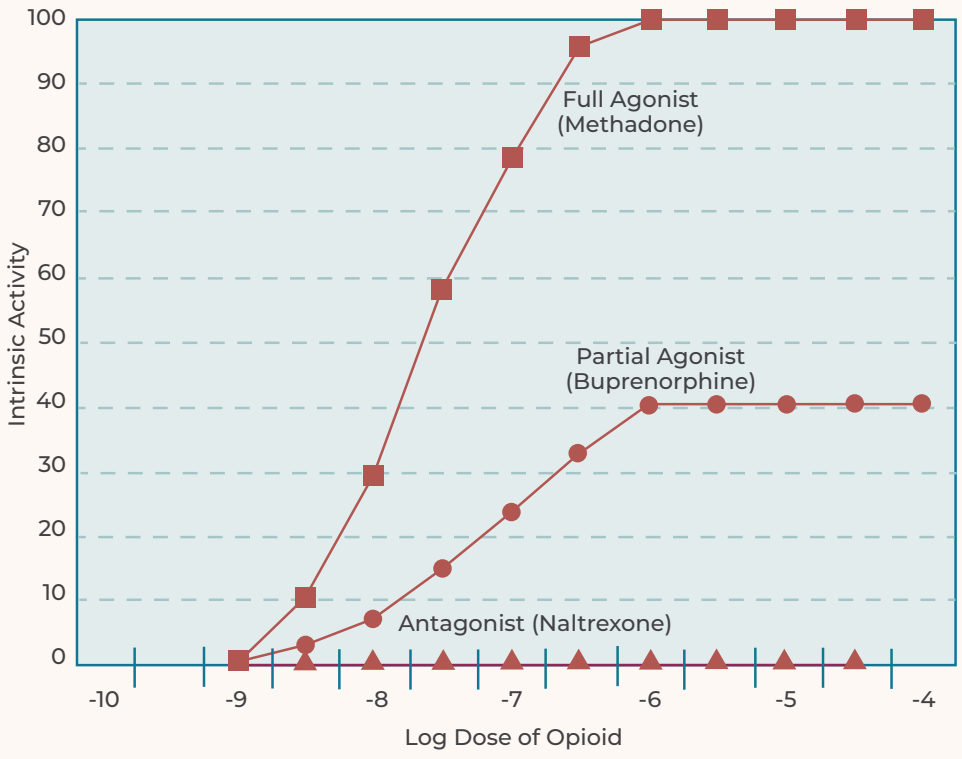

Exhibit 3A.5 summarizes OUD medication formulations, indications, and dosing.

The dosing guidance in subsequent chapters for methadone (Chapter 3B), naltrexone (Chapter 3C), and buprenorphine (Chapter 3D) is for healthcare professionals in general medical and addiction treatment settings. This guidance is based on:

- A review of the literature.
- A review of national and international organizations' guidelines.
- FDA-approved medication labels.
- The TIP expert panel's recommendations.

EXHIBIT 3A.5. OUD Medications: Formulations[74,75]

GENERIC/ TRADE NAME	FORMULATIONS	ACTION AT THE RECEPTOR	FDA INDICATIONS	DOSING REGIMEN
Methadone (Methadose, Dolophine)	Orally as liquid concentrate, tablet, or oral solution of powder or dispersible tablet	Mu-opioid receptor full agonist	Medically supervised withdrawal and maintenance treatment of opioid dependence; additional formulations FDA approved for pain are not a focus of this TIP	Once daily (also off-label dosing regimens if appropriate, such as split dose twice daily)
Generic buprenorphine monoproduct	Sublingual tablet, film	Mu-opioid receptor partial agonist	Treatment of opioid dependence; additional formulations FDA approved for pain are not a focus of this TIP	Once daily (also alternative off-label regimens)
Generic buprenorphine/ naloxone combination product	Sublingual tablet	Mu-opioid receptor partial agonist combined with mu-opioid receptor antagonist; the latter is not absorbed sublingually	Treatment of opioid dependence	Once daily (also alternative off-label regimens)
Buprenorphine/ naloxone (Zubsolv)	Sublingual tablet	Mu-opioid receptor partial agonist combined with mu-opioid receptor antagonist; the latter is not absorbed sublingually	Treatment of opioid dependence	Once daily (also alternative off-label regimens)
Buprenorphine/ naloxone (Bunavail)	Buccal film	Mu-opioid receptor partial agonist combined with mu-opioid receptor antagonist; the latter is not absorbed sublingually	Treatment of opioid dependence	Once daily (also alternative off-label regimens)

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EXHIBIT 3A.5. OUD Medications: Formulations (continued)

GENERIC/ TRADE NAME	FORMULATIONS	ACTION AT THE RECEPTOR	FDA INDICATIONS	DOSING REGIMEN
Buprenorphine/ naloxone (Suboxone)	Sublingual film; may also be administered buccally	Mu-opioid receptor partial agonist combined with mu-opioid receptor antagonist; the latter is not absorbed sublingually	Treatment of opioid dependence	Once daily (also alternative off-label regimens)
Buprenorphine (Probuphine)	Implants	Mu-opioid receptor partial agonist	Maintenance treatment of opioid dependence in clinically stable patients taking 8 mg/day or less of Suboxone equivalents	Implants last for 6 months and are then removed, after which a second set can be inserted
Extended-release injection buprenorphine (Sublocade)	Subcutaneous injection in the abdominal region	Mu-opioid receptor partial agonist	Treatment of moderate-to-severe OUD among patients initiated and taking transmucosal buprenorphine for at least 7 days	Monthly
Oral naltrexone (Naltrexone hydrochloride)	Oral tablet	Mu-opioid receptor antagonist	Block the effects of administered opioid agonists	Once daily (also alternative off-label regimens)
XR-NTX (Vivitrol)	Intramuscular injection	Mu-opioid receptor antagonist	Prevent return to opioid dependence after medically supervised opioid withdrawal	Once monthly by injection

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Chapter 3B: Methadone

Chapter 3B provides an overview of methadone pharmacology and discussion of key methadone dosing considerations for healthcare professionals working in opioid treatment programs (OTPs).

Methadone is the most studied pharmacotherapy for opioid use disorder (OUD). Of all OUD pharmacotherapies, it is used to treat the most people throughout the world and has by far the longest track record (nearly 50 years).[76,77] Numerous clinical trials and meta-analyses have shown that methadone treatment is associated with significantly higher rates of treatment retention and lower rates of illicit opioid use compared with placebo and with no treatment.[78] Other research associates methadone treatment with reduced mortality, criminal behavior, and HIV seroconversion.[79,80,81] A Cochrane meta-analysis found that, at flexible doses, methadone compared with buprenorphine retains patients in treatment significantly longer and equally reduces illicit opioid use.[82]

In the United States, OTPs can offer methadone to treat OUD, but all providers who may care for patients with OUD should be familiar with this treatment.

Formulations

There are several formulations of methadone:

- Liquid concentrate, which is the formulation most commonly used in treatment programs.
- Powder, which is dissolved in water and administered as a liquid.
- Dispersible tablets, which are scored tablets that are dissolved in water.
- Tablets, which are most commonly used outside of OTPs for analgesia.

Pharmacology

Methadone, a long-acting mu-opioid receptor full agonist, is a schedule II controlled medication. It is highly plasma–protein bound and binds to proteins within tissues throughout the body.[83] Through mu-opioid receptor binding and opioid cross-tolerance to other mu-opioid agonists, at adequate doses, **methadone reduces opioid craving and withdrawal and blunts or blocks the effects of illicit opioids.**

There is wide individual variability in methadone pharmacokinetics. The half-life of methadone can vary from 8 to 59 hours[84] depending on the patient. The average is 24 hours.[85]

Methadone has no ceiling effect. As a full agonist, increasing doses of methadone produce maximal physiological effects at the opioid receptors. Plasma levels reach steady state in about 5 days (i.e., five half-lives). Before achievement of steady state, release from tissue reservoirs can lead to increasing serum plasma levels and toxicity, even if the daily methadone dose is not changed.

Methadone induction, thus, should begin at a low dose and increase gradually with daily monitoring over days or weeks. At stable daily doses, serum levels peak 2 to 4 hours after dosing, then slowly decrease, providing 24 hours without overmedication or withdrawal.[86]

Bioavailability

Methadone is approximately 70 to 80 percent bioavailable when patients take it orally for OUD. There is notable individual variability in bioavailability, ranging from 36 to 100 percent.[87,88]

The liver's CYP450 3A4 enzyme is primarily responsible for metabolizing methadone,[89] although CYP2B6 and CYP2D6 enzymes are also involved.[90] At the start of methadone treatment, methadone can increase CYP3A4 activity and accelerate its own metabolism in some individuals.[91]

Dosing must be individualized because methadone's bioavailability, clearance, and half-life can vary considerably among patients.

Providers should check for potential drug–drug interactions and monitor patients receiving concomitant medications. Some medications (e.g., benzodiazepines, anticonvulsants, antibiotics, antiretroviral agents, some antidepressants) can induce or inhibit CYP450 enzymes, resulting in potential changes in methadone serum concentration, effectiveness, and side effect profile.

Dosing Considerations

Methadone is indicated for people meeting OTP admission criteria, which for people 18 and older are:

- Being currently "opioid-addicted"—the term the Substance Abuse and Mental Health Services Administration (SAMHSA) OTP regulations use (e.g., meeting *Diagnostic and Statistical Manual of Mental Disorders,* Fifth Edition,[92] criteria for OUD). Not all patients meeting OUD criteria, particularly those with mild OUD, are appropriate candidates for methadone. This is discussed in detail in Part 2 of this Treatment Improvement Protocol (TIP).
- Having a history of at least 1 year of opioid addiction before admission.
- Providing voluntary, written informed consent.

OTP physicians can waive the history requirement per Code of Federal Regulations (42 CFR 8.12)[93] for:

- Women who are pregnant.
- Former patients (up to 2 years after discharge).
- Patients within 6 months of release from incarceration.

For patients younger than 18, admission criteria are different. They include two documented, unsuccessful, medically supervised withdrawals or treatments without OUD medication (e.g., methadone) in a 12-month period. The parent or legal guardian must provide written informed consent.

Contraindications

Contraindications to treatment with methadone include an allergy to methadone and other instances in which opioids are contraindicated, such as acute asthma, in patients with abnormally high carbon dioxide blood levels (e.g., from pulmonary disease or sleep apnea), or paralytic ileus.

Precautions and Warnings

Respiratory depression

Methadone can cause respiratory depression, particularly during initial dosing and dose titration. The goal of methadone dosing in the first weeks of treatment (i.e., induction) is to relieve withdrawal but avoid oversedation and respiratory depression. Patients who are older or cachectic or who have chronic obstructive pulmonary disease are more susceptible to respiratory depression and should be treated cautiously with lower doses.

> **A standard formula for dose induction for all patients, without careful monitoring of response to treatment, and individualized dose adjustment is inadvisable. This can lead to methadone intoxication and overdose death.**

Individualize dosing decisions through daily monitoring of patients' responses to treatment. Opioid tolerance cannot be accurately gauged based on patient self-reports of the type, amount, or purity of the opioids they've used or of the severity of their opioid withdrawal symptoms.

The best approach to dosing is to start low and go slow. Methadone has a relatively long half-life (24–36 hours or longer). Steady-state serum levels are generally not reached until about five half-lives. **This means that patients will not feel the full effect of the initial dose for 4 or more days** even if the daily dose is the same. Slow release of methadone from tissues causes serum levels to continue to increase until reaching steady state. Initially a dose may seem appropriate, but the third or fourth day of the same dose can lead to oversedation and even respiratory depression and death.[94]

Use a lower-than-usual starting dose in individuals with no or low opioid tolerance (5 mg to 10 mg). Increase doses slowly and with careful monitoring for patients who:

- Have not used opioids for 5 or more days (e.g., after leaving a controlled environment).
- Do not use opioids daily.
- Use weaker opioids (e.g., codeine).

Do not determine doses by analgesic equivalence dose conversion tables for patients using high doses of prescription opioids, whether by prescription or illicitly. This can lead to death owing to incomplete cross-tolerance[95] and the unique pharmacology of methadone.

Concurrent substance use disorders (SUDs) involving benzodiazepines or alcohol

Concurrent misuse of alcohol or benzodiazepines with methadone (or buprenorphine) increases respiratory depression risk. Use of alcohol and benzodiazepines (illicit and prescription) is common in patients with OUD. Managing OUD with methadone for patients with alcohol or benzodiazepine use disorders is challenging and should be undertaken with care. A 2017 Food and Drug Administration (FDA) Drug Safety Communication noted that although concomitant use of buprenorphine or methadone with benzodiazepines increases the risk of an adverse reaction, including overdose death, opioid agonist treatment should not be denied to patients solely on the basis of their taking benzodiazepines, because untreated OUD can pose a greater risk of morbidity and mortality.[96] FDA advises that careful medication management by healthcare professionals can reduce risk (see www.fda.gov/downloads/Drugs/DrugSafety/UCM576377.pdf for more information).

Strategies to manage patients with concurrent alcohol or benzodiazepine use disorders include the following (see also Exhibit 3B.1):

- **Obtain permission to communicate with the benzodiazepine prescriber** to confirm the reason for use, adherence to treatment, and prescriber awareness of the patient's OUD. It can also help to speak (with permission) with close family members or friends to assess the extent and impact of any alcohol or benzodiazepine misuse.
- **Ensure that patients understand the risk** of potential respiratory depression and unintentional overdose death when combining methadone with alcohol, benzodiazepines, or other central nervous system (CNS) depressants.
- **Determine whether patients require medically supervised withdrawal or tapering from alcohol or benzodiazepines.** Patients at risk for serious alcohol or benzodiazepine withdrawal syndrome (including seizures and delirium tremens) may need inpatient medically supervised withdrawal.
- **Attempt gradual outpatient medically supervised withdrawal for benzodiazepines when indicated.** Some OTPs have the staffing and capacity to provide a supervised

EXHIBIT 3B.1. Strategies for Managing Benzodiazepine Use by Patients in OUD Treatment

- **Carefully assess the patient's benzodiazepine use,** including:
  - Intent of use.
  - Source (check the state's prescription drug monitoring program [PDMP]).
  - Amount and route of use.
  - Binge use.
  - Prior overdoses.
  - Harms (e.g., car crashes, criminal acts, sleep trouble).
  - Co-use with other substances that further increase risk for respiratory depression and overdose.
  - Withdrawal history (e.g., seizures, delirium).
- **Also assess for:**
  - Psychiatric and medical comorbidity.
  - Motivation for change.
  - Psychosocial support system (obtain history from a significant other if the patient permits).
- **Gauge level of care and setting needed** (e.g., residential, outpatient). Inpatient treatment may be best for patients with poor motivation, limited psychosocial support, serious or complicated comorbidity, or injection or binge use.
- **Coordinate with other prescribers.** 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.
- **Address comorbid mental disorders** (e.g., anxiety, depression) with other medications or psychosocial treatments, when feasible.
- **Provide medically supervised withdrawal** from benzodiazepines or refer to specialty care for same.
- **Create a treatment plan with built-in conditions** (e.g., urine testing, more frequent visits, short medication supply).
- **Frequently review patient progress and objective outcomes,** such as:
  - Urine drug testing.
  - PDMP reports.
  - Psychosocial functioning.
  - Reports from significant others.
- **Revise treatment plans** as needed, and document the rationale for treatment decisions.

Adapted with permission.[97]

outpatient taper from benzodiazepines. This usually requires use of a long-acting benzodiazepine, management of anxiety and sleeplessness, and careful monitoring with observed dosing and toxicology screening. It may also require lower-than-usual methadone doses. Engage in outpatient medically supervised withdrawal only with patients who are physically dependent on benzodiazepines but do not inject or binge. This may only be successful in a minority of patients. Attempt the taper while continuing treatment with methadone, subject to certain conditions that promote safety and reduce risk.

- **Consider increasing counseling frequency as appropriate.**

For more information on managing benzodiazepine use, see *Management of Benzodiazepines in Medication-Assisted Treatment* (http://ireta.org/wp-content/uploads/2014/12/BP_Guidelines_for_Benzodiazepines.pdf).

QTc prolongation and cardiac arrhythmia

Methadone treatment has been associated with QTc prolongation, which often occurs without clinical consequences.[98,99] Since 2006, methadone has had an FDA black box warning on QTc prolongation and Torsades de Pointes. QTc intervals above 500 milliseconds can increase risk for this rare ventricular arrhythmia, which can be lethal.[100,101] The prevalence of QTc prolongation among methadone patients is

QTc prolongation is an abnormally long time in electrocardiogram (ECG) tracing between the start of a Q wave and the end of a T wave. Various cutoffs define prolonged QTc interval, including greater than 450 milliseconds for men, greater than 460 to 470 milliseconds for women, or greater than 450 milliseconds for either gender.[102] However, the faster the heart rate, the shorter the QTc interval. Hence, correct the QTc interval for heart rate; divide the QTc interval in milliseconds by the square root of the R-R interval in seconds.[103]

not known with certainty. It has been estimated that about 2 percent of patients in methadone treatment have QTc intervals greater than 500 milliseconds.[104] According to methadone's FDA label, most Torsades de Pointes cases occur in patients receiving methadone for pain treatment, although some cases have occurred among those in methadone maintenance.[105] High methadone doses may be associated with prolonged QTc intervals.[106] Other risk factors include:[107]

- Some medications (e.g., antidepressants, antibiotics, antifungals).
- Congenital prolonged QTc interval.
- Hypokalemia.
- Bradycardia.

There is considerable controversy about how best to screen for QTc prolongation without creating barriers to methadone treatment entry.[108] Indeed, a Cochrane review of the literature was unable to draw any conclusions about the effectiveness of QTc screening strategies in preventing cardiac morbidity or mortality among methadone patients.[109] Notwithstanding the uncertainty about the best approach, OTPs can take steps to identify patients who may be at risk for cardiac arrhythmia. **The TIP expert panel concurs with the recommendations of other expert panels (which included cardiologists) that OTPs develop a cardiac risk management plan,**[110,111] to the extent possible. **OTPs should consider the following elements in crafting a cardiac risk management plan:**

- **An intake assessment of risk factors, which can include:**
  - Family history of sudden cardiac death, arrhythmia, myocardial infarction, heart failure, prolonged QTc interval, or unexplained syncope.
  - Patient history of arrhythmia, myocardial infarction, heart failure, prolonged QTc interval, unexplained syncope, palpitations, or seizures.
  - Current use of medications that may increase QTc interval (for a complete list, see https://crediblemeds.org/pdftemp/pdf/CombinedList.pdf; register for free for the most current list).
  - Patient history of use of cocaine and methamphetamines (which can prolong the QTc interval).
  - Electrolyte assessment (for hypokalemia or hypomagnesemia).
- **A risk stratification plan, which can include the following:**
  - **Conduct an ECG for patients with significant risk factors** at admission; repeat within 30 days. Repeat once a year and if the patient is treated with more than 120 mg of methadone per day.
  - Discuss risks and benefits of methadone with patients with QTc intervals between 450 and 500 milliseconds. Adjust modifiable risk factors to reduce their risk.
  - **Do not start methadone treatment for patients with known QTc intervals above 500 milliseconds.** If such an interval is discovered during treatment, have a risk/benefit discussion. Strongly consider lowering the methadone dose, changing concurrent medications that prolong the

QTc interval, eliminating other risk factors, and, if necessary, switching to buprenorphine. Include follow-up ECG monitoring.
- Consider providing routine universal ECG screening if feasible, although there is insufficient evidence to formally recommend doing so.[112]

Accidental ingestion

Inform patients that accidental ingestion can be fatal for opioid-naïve individuals, particularly children. Patients should safeguard take-home methadone in a lockbox out of the reach of children.

Neonatal abstinence syndrome (NAS)

Ensure awareness among pregnant patients or patients who may become pregnant that NAS can occur in newborns of mothers treated with methadone. Women receiving methadone treatment while pregnant should talk with their healthcare provider about NAS and how to reduce it. Research has shown that the dose of opioid agonist medication is not reliably related to the severity of NAS.[113,114,115] Thus, each woman should receive the dose of medication that best manages her illness.

Misuse and diversion

Alert patients to the potential for misuse and diversion of methadone.

Physical dependence

Inform patients that they will develop physical dependence on methadone and will experience opioid withdrawal if they stop taking it.

Sedation

Caution patients that methadone may affect cognition and psychomotor performance and can have sedating effects. Urge patients to be cautious in using heavy machinery and driving until they are sure that their abilities are not compromised.

Adrenal insufficiency

Adrenal insufficiency has been reported in patients treated with opioids. Ask patients to alert healthcare providers of nausea, vomiting, loss of appetite, fatigue, weakness, dizziness, or low blood pressure.[116]

Drug Interactions

Methadone has more clinically significant drug–drug interaction than buprenorphine.[117] Carefully monitor each patient's response to treatment if they are prescribed or stop taking a CYP450 34A inducer or inhibitor. Methadone dosages may need to be adjusted up or down depending on the medication and whether treatment is starting or stopping. Exhibit 3B.2 lists common interactions between methadone and other medications.

Medications that induce CYP450 activity can increase methadone metabolism. Patients may experience craving or opioid withdrawal symptoms between doses if they begin these medications or become sedated if they discontinue them:

- Some antibiotics (e.g., rifampin).
- Antiretrovirals (e.g., efavirenz, nevirapine, ritonavir).
- Anticonvulsants (carbamazepine, phenobarbital, phenytoin).

Other medications can inhibit CYP450 activity and decrease methadone metabolism, causing symptoms of overmedication (e.g., sedation) when the medication is started and possibly withdrawal or cravings when it is stopped. Among such medications are:[118]

- Some antibiotics (ciprofloxacin, erythromycin).
- Antacids (cimetidine).
- Antifungals (fluconazole).
- Antidepressants (e.g., fluvoxamine, paroxetine, sertraline).

Methadone can affect the metabolism of other medications. For example, zidovudine levels are reported to increase significantly during

EXHIBIT 3B.2. Common Potential Methadone Drug–Drug Interactions

Antiretrovirals

CLASS OR SPECIFIC DRUG	INTERACTION	PUTATIVE MECHANISM	NOTES
Efavirenz, lopinavir, nevirapine	Reduction in serum methadone levels	Induction of CYP450 enzymes	Clinically significant opioid withdrawal symptoms likely
Abacavir, etravirine, nelfinavir, ritonavir, saquinavir, tipranavir	May reduce serum methadone levels	Induction of CYP450 enzymes	Clinically pertinent opioid withdrawal symptoms unlikely
Didanosine	Reduction in didanosine plasma concentrations	Decreased bioavailability	Possible decreased efficacy of didanosine
Zidovudine	Increase in zidovudine plasma concentration	Unknown	Risk of zidovudine toxicity

Antidepressants

CLASS OR SPECIFIC DRUG	INTERACTION	PUTATIVE MECHANISM	NOTES
Tricyclic: Amitriptyline, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine	Increased risk for constipation, sedation, QTc prolongation, and arrhythmia	Anticholinergic effects; blockade of human ether-a-go-go-related gene (hERG) channel	Clinical experience with combination indicates it is generally safe with careful clinical monitoring
Serotonin reuptake inhibitors: citalopram, escitalopram, fluvoxamine, fluoxetine, paroxetine, sertraline	May increase serum methadone levels; increased risk for serotonin syndrome	Inhibition of CYP enzymes; blockade of serotonin transporter	Clinical experience with combination indicates it is generally safe with careful clinical monitoring
Monoamine oxidase inhibitors: Isocarboxazid, phenelzine, selegiline, tranylcypromine	Increased risk for serotonin syndrome	Inhibition of serotonin metabolism	Avoid or use with extreme caution and careful clinical monitoring
Serotonin/norepinephrine reuptake inhibitors: Duloxetine, desvenlafaxine, venlafaxine	Increased risk for serotonin syndrome; increased risk for QTc prolongation and arrhythmia (venlafaxine)	Blockade of serotonin transporter; blockade of hERG channel (venlafaxine)	Clinical experience with combination indicates it is generally safe with careful clinical monitoring

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EXHIBIT 3B.2. Common Potential Methadone Drug–Drug Interactions (continued)

Antibiotics

CLASS OR SPECIFIC DRUG	INTERACTION	PUTATIVE MECHANISM	NOTES
Ciprofloxacin, clarithromycin, erythromycin, azithromycin	May increase methadone serum levels; increased risk for QTc prolongation and arrhythmia	Inhibition of CYP enzymes; blockade of hERG channel	One case report of sedation (ciprofloxacin); clinical monitoring required
Rifampin	Reduction in serum methadone levels	Induction of CYP enzymes	Severe opioid withdrawal can occur; need increased methadone dose

Antifungals

CLASS OR SPECIFIC DRUG	INTERACTION	PUTATIVE MECHANISM	NOTES
Ketoconazole, fluconazole	May increase methadone serum levels	Inhibition of CYP enzymes	Little evidence for important clinical effects

Anticonvulsants

CLASS OR SPECIFIC DRUG	INTERACTION	PUTATIVE MECHANISM	NOTES
Carbamazepine, phenytoin, phenobarbital	Reduction in serum methadone levels	Induction of CYP enzymes	Severe opioid withdrawal can occur; will need increased methadone dose

Antiarrhythmics

CLASS OR SPECIFIC DRUG	INTERACTION	PUTATIVE MECHANISM	NOTES
Procainamide, quinidine	Increases risk for QTc prolongation and arrhythmia	Blockade of hERG channel	Careful clinical monitoring required
Amiodarone	May increase methadone serum levels; increased risk for QTc prolongation and arrhythmia	Inhibition of CYP enzymes; blockade of hERG channel	Careful clinical monitoring required

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EXHIBIT 3B.2. Common Potential Methadone Drug–Drug Interactions (continued)

Other Drugs and Specific Classes

CLASS OR SPECIFIC DRUG	INTERACTION	PUTATIVE MECHANISM	NOTES
Benzodiazepines	Additive CNS and respiratory depressant effects	Increased GABA activity	Careful clinical monitoring required
Barbiturates	Additive CNS and respiratory depressant effects	Increased GABA activity	Careful clinical monitoring required
Cimetidine	May increase serum methadone levels	Inhibition of CYP enzymes	No evidence of major clinical effect
Naltrexone	Precipitated opioid withdrawal	Displaces methadone from mu-opioid receptors	Contraindicated

Adapted with permission.[119]

methadone treatment. Monitoring for zidovudine side effects during treatment is warranted.[120] Check drug–drug interactions online (www.drugs.com/drug_interactions.php).

Side Effects

Possible side effects of methadone include the following (methadone FDA labels list all potential side effects and are available at https://dailymed.nlm.nih.gov/dailymed/search.cfm?labeltype=all&query=METHADONE):

- Constipation
- Nausea
- Sweating
- Sexual dysfunction or decreased libido
- Drowsiness
- Amenorrhea
- Weight gain
- Edema

Assessment

A thorough assessment will help decide whether a patient is appropriate for admission and meets federal and any state regulatory requirements for methadone treatment. (See Part 2 of this TIP for detailed discussion of screening and assessment.) **Before ordering methadone:**

- **Check the state PDMP** for opioid or benzodiazepine prescriptions from other providers (see www.nascsa.org/stateprofiles.htm for links to state PDMPs). Note that methadone for OUD treatment will not appear in the PDMP because of confidentiality regulations regarding substance use treatment records. Obtain the patient's consent to release information and speak with treating providers to coordinate care for patient safety.
- **Take 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 recency (last day of use and use in the past 30 days).
  - Establish OUD diagnosis.
  - Assess for other SUDs, including those that involve alcohol, benzodiazepines, or stimulants.

- **Conduct a physical exam.**
  - **Assess for signs and symptoms of intoxication.** Do not give patients who are sedated or intoxicated their first dose. Instead, assess and treat them appropriately:
    - Identify causes of sedation or intoxication.
    - Ensure the patient's immediate safety.
    - Reassess methadone induction appropriateness.
    - Develop a plan to reattempt induction or follow a different course of treatment as appropriate.
  - **Assess for signs and symptoms of opioid withdrawal and physiological dependence.** One approach to documenting withdrawal symptoms is to use a scale such as the Clinical Opioid Withdrawal Scale (COWS) or the Clinical Institute Narcotic Assessment (CINA) Scale for Withdrawal Symptoms (see "Resource Alert: Opioid Withdrawal Scales"). Before the first dose of methadone, confirm signs of opioid withdrawal to provide some confidence that the patient is opioid tolerant and can begin dose induction. The Naloxone Challenge should not be routinely used to determine physiologic withdrawal because withdrawal symptoms will be visible, if present, on physical exam if enough time has passed since last opioid use.[121]

- **Obtain laboratory tests.**
  - **Conduct drug and alcohol tests.** Use reliable urine tests for drugs, including opioids (e.g., morphine, methadone, buprenorphine, oxycodone), benzodiazepines, cocaine, and other drugs that may be commonly used in the area (e.g., methamphetamine). Obtain an opioid urine or oral fluid test before initiating treatment. A negative opioid test in the absence of clear opioid withdrawal symptoms indicates that the patient is likely no longer opioid tolerant; diagnosis should be reconfirmed. If such patients are to start taking methadone (rather than naltrexone for relapse prevention), use caution in initiating treatment (see the subsection "First dose for patients without current opioid tolerance" in the section "Initiating Methadone Treatment"). Use an alcohol breathalyzer to estimate the patient's blood alcohol content. Do not provide methadone until the alcohol reading is considerably below the legal level of alcohol intoxication.

RESOURCE ALERT

Opioid Withdrawal Scales

The COWS and other opioid withdrawal scales from Annex 10 of the World Health Organization's *Guidelines for the Psychosocially Assisted Pharmacological Treatment of Opioid Dependence* can be downloaded from the National Center for Biotechnology Information website (www.ncbi.nlm.nih.gov/books/NBK143183).

The CINA Scale for Withdrawal Symptoms also is available online (https://ncpoep.org/wp-content/uploads/2015/02/Appendix_7_Clinical_Institute_Narcotic_Assessment_CINA_Scale_for_Withdrawal_Symptoms.pdf).

- **Conduct a pregnancy test.** Pregnant patients with OUD should be treated with methadone or transmucosal buprenorphine.[122,123] Discuss risks and benefits of treatment with methadone and alternative approaches for each patient and fetus versus the risks of continued illicit opioid use. Refer pregnant patients to prenatal care. Women should be advised that their menstrual cycle may return to normal once they are stabilized on medication, and hence they should use birth control if they wish to avoid pregnancy.
- **Conduct liver function tests.** If possible, assess liver function tests. It is not necessary to wait for the results of these tests to begin treatment, because the risk of not starting methadone outweighs the benefits of having the test results. Patients with suspected cirrhosis based on history and clinical exam should be started at a lower methadone dose than typical patients, with more cautious titration. Patients who have chronic hepatitis can be treated with methadone. Have a risk/benefit discussion with patients whose liver enzymes are at or greater than five times the normal level and monitor their liver function during treatment.
- **Conduct hepatitis and HIV testing.** Hepatitis B and C are common among patients who enter methadone treatment. HIV infection is also prevalent. Everyone ages 15 to 65 should be tested at least once for HIV. Persons at higher risk, such as people who use drugs by injection, should be tested annually.[124] Anyone who is injecting or has ever injected drugs, even once, no matter how long ago, should be tested for hepatitis C, regardless of their intention to seek treatment for SUD.[125] The Centers for Disease Control and Prevention recommends hepatitis B vaccination for people seeking treatment for SUDs.[126]

Patient Selection

No evidence clearly predicts which patients will respond best to methadone treatment versus alternative pharmacotherapies. Inform patients of all options and the settings in which they're available, as appropriate. (See "Treatment Planning or Referral" in Part 2 of this TIP for more on shared decision making.)

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

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

Pregnant women should be considered for methadone treatment.

Methadone (or buprenorphine) treatment through OTPs may be best for patients who need a higher level of outpatient structure or supervision of medication adherence. Tailor medication decisions to patients' medical and substance use histories, patient preferences, and treatment availability.

Informed Consent

Inform all patients of:

- Their OUD diagnosis and the nature of the disorder.
- Risks and benefits of methadone and other OUD medications.
- Risks and benefits of nonmedication treatments.

> 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 3B.3. Key Points of Patient Education for Methadone

Before starting OUD treatment with methadone, patients should:

- Be told that the methadone dose is started low and increased slowly over days and weeks with monitoring, because it takes 4 or more days for the body to adjust to a dose change. This is necessary to avoid the risk of overdose.
- Understand that the goal of the first weeks of treatment is to improve withdrawal symptoms without oversedation. Patients should inform providers if they feel sedated or "high" within the first 4 hours after their dose.
- Learn the symptoms of methadone intoxication and how to seek emergency care. The first 2 weeks of treatment have the highest risk of overdose.
- Be aware that rescue naloxone does not last very long, so they should remain in emergency care for observation if they are treated for opioid overdose.
- Know that concurrent alcohol, benzodiazepine, or other sedative use with methadone increases the risk of overdose and death.
- Inform OTP nursing/medical staff about prescribed and over-the-counter medications and herbs (e.g., St. John's wort) they are taking, stopping, or changing doses of to allow assessment of potential drug–drug interactions.
- Inform other treating healthcare professionals that they are receiving methadone treatment.
- Plan to avoid driving or operating heavy machinery until their dose is stabilized.
- Learn about other possible side effects of methadone, including dizziness, nausea, vomiting, sweating, constipation, edema, and sexual dysfunction.
- Agree to keep take-home doses locked up and out of the reach of others. Understand that giving methadone, even small amounts, to others may be fatal.
- Inform providers if they become pregnant.
- Understand that stopping methadone increases their risk of overdose death if they return to illicit opioid use.

Patients should sign consent forms before starting treatment. The Chapter 3B Appendix provides a sample consent form for treatment in an OTP.

Educate patients about what to expect when receiving methadone treatment (Exhibit 3B.3). Caution them against using alcohol and drugs during methadone treatment. Warn them of the increased risk of overdose during the first 2 weeks of treatment. Also warn them that discontinuing treatment and returning to opioid use will increase their risk of overdose. Document patient education in the medical record.

Educate patients about the importance of safe storage of take-home methadone doses. Discuss with patients where they will store their take-home medication. Advise them against storing medication in common areas of the home

RESOURCE ALERT

Patient and Family Member Educational Resources

Decisions in Recovery: Treatment for Opioid Use Disorder offers information for patients on the use of medications for OUD (https://store.samhsa.gov/product/SMA16-4993)

Medication-Assisted Treatment for Opioid Addiction: Facts for Families and Friends offers information for family members and friends (https://mha.ohio.gov/Portals/0/assets/HealthProfessionals/About%20MH%20and%20Addiction%20Treatment/MAT/SMA14-4443.pdf?ver=2018-11-26-113004-157)

where visitors or children would have access, such as kitchens and bathrooms. Take-home doses should be kept in their original childproof packaging in a lockbox. The key should not be left in the box. Inform patients that any portion of a dose taken by another person, a child, or pet can be deadly. If this occurs, call 9-1-1 immediately.

Initiating Methadone Treatment

Observing patients directly when they take doses early in treatment is not just required; it's beneficial. It maximizes adherence, provides a daily opportunity to assess response to the medication, and minimizes the likelihood of medication diversion. Federal OTP regulations permit patients to receive one take-home dose per week, given routine clinic closure on weekends. Patients who demonstrate progress can earn one additional take-home dose per week for the first 90 days of treatment at the OTP medical director's discretion. All other doses are directly observed at the clinic in the first 90 days.

The goal of initiating methadone treatment is to increase the patient's methadone dose gradually and safely, stabilizing the patient and reducing his or her opioid use while recognizing that the risk of dropout or overdose from illicit opioid use may increase if induction is too slow.

Day 1

The first dose should reduce opioid withdrawal symptoms. Perform induction cautiously; it's impossible to judge a patient's level of tolerance with certainty. For patients addicted to prescription opioids, opioid conversion tables should not be relied on to determine methadone dosage.

First dose for patients with opioid tolerance

The first dose for patients tolerant to opioids is generally between 10 mg and 30 mg (30 mg is the maximum first dose per federal OTP regulations). After the first dose, patients should remain for observation for 2 to 4 hours if possible to see whether the dose is sedating or relieves withdrawal signs.

- If withdrawal symptoms lessen, the patient should return the next day to be reassessed and to continue the dose induction process.
- If sedation or intoxication occurs after the first dose, the patient should stay under observation at the clinic until symptoms resolve. In this case, the patient should be reassessed the following day, and the subsequent day's dose should be substantially reduced. Extremely rarely, the patient will need to be treated for overdose with naloxone. If necessary, begin rescue breathing and call 9-1-1.
- If the patient shows neither sedation nor reduction of objective signs of opioid withdrawal during the 2- to 4-hour waiting period, administer another 5 mg dose. A final 5 mg dose after another waiting period of 2 to 4 hours can be administered if necessary. The maximum total methadone dose on the first day of treatment should not exceed 40 mg.[127] However, caution dictates against exceeding a total first day's dose of 30 mg except in rare cases. In such cases, the patient should be carefully monitored on subsequent days to rule out oversedation.
- Patients transferring from another OTP whose methadone dose and last date of medication administration can be confirmed by the medical staff and documented in the medical record can be continued on the same methadone dose administered in the original OTP, even if the dose exceeds the maximum permitted 40 mg.

For some patients, the lower range of initial doses is best. Dose with 10 mg to 20 mg in patients who:

- Are ages 60 and older.
- May have lower levels of opioid tolerance based on their recent history.
- Use sedating medications, such as benzodiazepines, antipsychotics, or antidepressants.
- Engage in problem drinking or have alcohol use disorder.
- Take medications that can increase methadone serum levels or are stopping medications that decrease methadone serum levels.[128]

- Have medical disorders that may cause hypoxia, hypercapnia, or cardiac arrhythmias. These include:
  - Asthma, chronic obstructive pulmonary disease, and kyphoscoliosis.
  - Obesity.
  - Sleep apnea.
  - QTc prolongation.
  - A family history of cardiac arrhythmias, fainting or dizziness, or sudden death.
  - Cor pulmonale.
  - Electrolyte abnormalities, such as hypokalemia or hypomagnesemia.

First dose for patients without current opioid dependence

In some circumstances, patients who are not currently dependent on opioids may be admitted to an OTP (e.g., individuals with a history of OUD who are returning from controlled environments).[129] In these instances, consider treatment with extended-release naltrexone (XR-NTX) to avoid establishing new physiological opioid dependence. Instead of starting methadone, consider starting with a low dose of buprenorphine because of buprenorphine's superior safety threshold.[130] In one such study, 1 mg of buprenorphine was the starting dose, which was increased slowly[131] (see Chapter 3D of this TIP). If XR-NTX and buprenorphine are not available, or the patient prefers methadone treatment, consider starting methadone at a 5 mg daily dose (as was done in one study[132]) after discussing risks and benefits with the patient.

Titrate the dose much more slowly than for patients who are opioid tolerant. Increase initially by 5 mg about every week, based on patient response. Doses can be increased somewhat more rapidly after careful assessment of response if the patient begins to use illicit opioids. As with other methadone dosing, induction in these cases should not be based on a standing order.

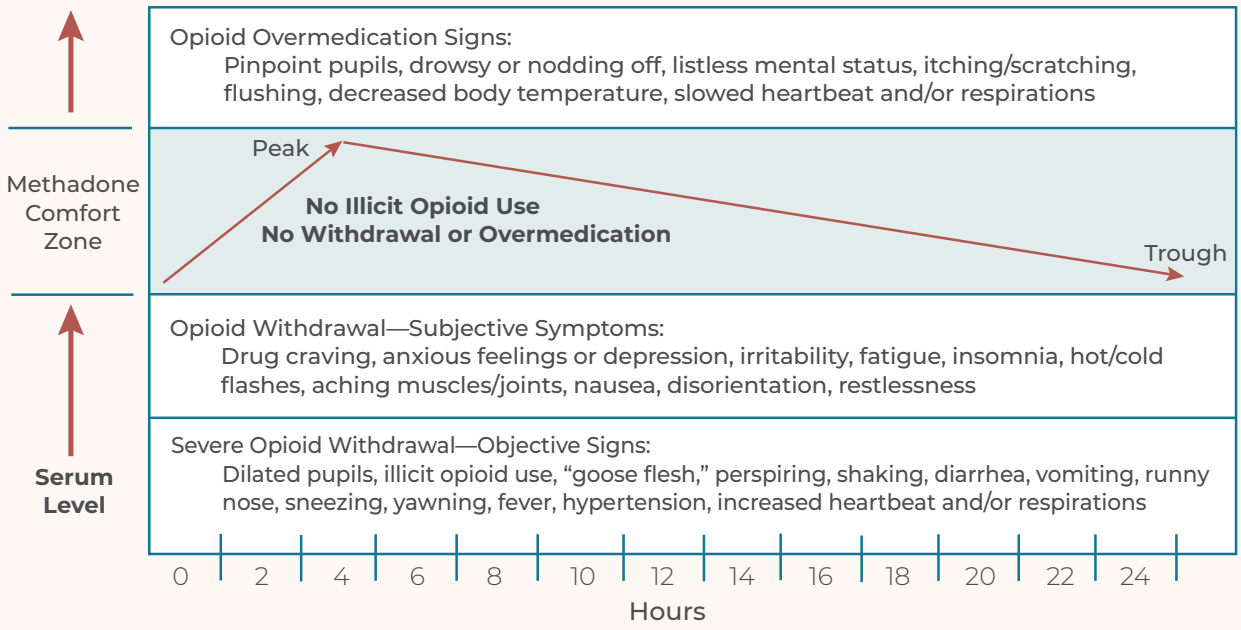
Dose Titration (Weeks 1 to 2)

The goals of early dose titration for patients with current opioid dependence starting on Day 2 of the first week of treatment through stabilization are to avoid sedation at peak serum levels and to gradually extend time without opioid withdrawal symptoms and craving. When patients attend the program, before dose administration, nursing and/or medical staff members should ask patients whether they felt sedation, opioid intoxication effects, or opioid withdrawal symptoms 2 to 4 hours after their methadone administration the prior day (Exhibit 3B.4). Doses should be decreased for reports of symptoms of opioid intoxication or oversedation. **Dosing must be individualized based on careful patient assessment and generally should not be increased every day, because plasma methadone levels do not reach steady state until about five methadone half-lives (Exhibit 3B.5).**

Even when holding the methadone dose constant over several days, the patient's methadone serum level will rise each day until it reaches steady state (Exhibit 3B.5). For example, if the patient remains on 20 mg per day for the first few days of induction, the serum level on Day 2 would reflect the 20 mg second day's dose plus 10 mg that remained in the body from the first day's dose (for the equivalent single dose total of 30 mg). The third day would reflect the 20 mg third day's dose, plus 10 mg remaining in the body from the second day's dose, and 5 mg remaining from the first day's dose (for the equivalent single dose total of 35 mg), and so on. **Patients who report relief from withdrawal 4 to 12 hours after their last dose may benefit from staying at that same dose for a few days** so that their serum level can stabilize.[133]

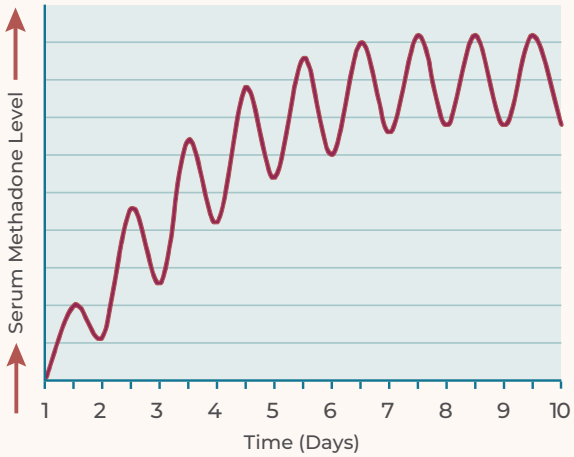
An American Society of Addiction Medicine expert panel recommended increasing the methadone dose in this phase by 5 mg or less every 5 or more days.[134] Other expert recommendations suggest somewhat faster dose increases,[135] including increases of 5 mg to 10 mg no sooner than every 3 to 4 days.[136,137] The

EXHIBIT 3B.4. Using Signs and Symptoms To Determine Optimal Methadone Level



Adapted with permission.[138]

EXHIBIT 3B.5. Steady-State Methadone Concentration Reached in About 5 Days



Adapted with permission.[139,140]

most important principle is to individualize dose induction based on careful assessment of the patient's response to the medication.

Dose Titration (Weeks 3 to 4)

Methadone doses can be increased further in 5 mg increments about every 3 to 5 days based on the patient's symptoms of opioid withdrawal or sedation.[141] Patients who miss more than four doses must be reassessed. Their next methadone dose should be decreased substantially and built back up gradually. It may be necessary to restart the dose induction process from Day 1. Be aware of any specific state requirements regarding missed doses.

Serum Levels

Dosing must be individualized because methadone's bioavailability, clearance, and half-life vary among patients, affecting their clinical

responses and requiring doses to be changed. Many factors can affect serum levels and clinical responses to treatment. Along with age and diet, these factors include:

- Other medications and herbs (e.g., St. John's wort).
- Genetic differences in metabolizing enzymes.
- Pregnancy.
- Changes in urinary pH.[142]

Consider measuring serum methadone levels in patients who, after being on a stable methadone dose, report feeling drowsy 2 to 4 hours after dose administration but develop craving or withdrawal symptoms before the next dose is due to be administered. This may occur in the third trimester of pregnancy, when concomitant medications interact with methadone, or when patients rapidly metabolize opioids. In such cases, consider dividing the daily methadone dose into twice-daily dosing.[143]

To assess serum methadone levels, draw peak and trough blood specimens at about 3 hours and 24 hours, respectively, after dose administration. Serum methadone levels generally correlate with methadone dose,[144] but there is no defined therapeutic window based on serum methadone level because response varies widely among patients. Minimum trough methadone levels of 300 ng/mL to 400 ng/mL may be associated with reduced likelihood of heroin use,[145] but determining the therapeutic dose should depend on the overall patient response, not the serum plasma levels. Peak:trough ratios above 2:1 may indicate rapid metabolism.[146]

Dose Stabilization (Week 5 and Beyond)

Once the patient achieves an adequate dose, extended continuation is possible without dose adjustment. Continuing treatment goals are to avoid sedation, eliminate withdrawal and craving, and blunt or block euphoric effects of illicit opioids.

> **The TIP expert panel advises against arbitrary methadone dosage caps.**

There may be reasons to further adjust the dose, including:

- Changes in health that can affect medications (e.g., acute hepatitis, exacerbation of pulmonary disease, sleep apnea).
- Changes in patient medications.
- Pregnancy. Increased metabolism in the last trimester may warrant dose increase or split dosing.[147,148] This may require a SAMHSA exception for daily take-home half-doses via an SMA-168 Exception Request (www.samhsa.gov/medication-assisted-treatment/opioid-treatment-programs/submit-exception-request).
- Concurrent illicit opioid or other drug or alcohol use.

As illicit opioid use stops and stabilization is achieved, the patient may wish to lower the dose to reduce any unpleasant side effects. Typical stabilization doses of at least 60 mg are associated with greater treatment retention; 80 mg to 120 mg[149] is the typical daily range.[150] However, there is wide variation, and some patients benefit from higher daily doses.

Take-Home Medication

OTPs can provide gradually increasing numbers of take-home doses to patients who discontinue illicit drug use and begin achieving treatment goals, commensurate with their tenure in the program. This provides a powerful incentive for patients to achieve treatment goals.[151] It also furthers patients' recovery goals by allowing them to attend work, school, or other activities without daily OTP visits.

Federal OTP regulations describe the conditions under which take-home doses are permitted. Some states have additional regulations. OTPs should be familiar with these regulations and have written procedures to address take-home dosing.

The benefits of take-home doses must outweigh the risks and further patients' rehabilitation goals. When deciding whether patients can handle the responsibility of take-home doses of methadone or buprenorphine, OTP medical directors should consider whether patients demonstrate:

- No recent misuse of substances.
- Regular clinic attendance.
- No serious behavioral problems at the clinic.
- No recent criminal activity (e.g., selling drugs).
- Stability at home and in social relationships.
- Sufficient time in treatment.
- Ability and intent to store take-home medication safely.
- Rehabilitative benefits from decreasing the frequency of clinic attendance that outweigh the potential risks of diversion.

Federal regulations based on patients' time in treatment determine eligibility to be considered for receiving take-home doses of methadone (but buprenorphine is not bound by these limits):

- One earned dose/week (beyond a weekly clinic closure day or federal holiday, when clinics typically close) in the first 90 days of treatment
- Two doses during the second 90 days
- Three doses during the third 90 days
- Up to 6 doses during the last 90 days
- Up to 2 weeks of doses after 1 year
- Up to 1 month of doses after 2 years

Assessing responsible handling of take-home doses

Methadone diversion is a risk. People with OUD who are not in treatment more frequently use illicit methadone to self-medicate withdrawal symptoms than to achieve euphoria.[152,153] Still, diversion is a public health risk; people who self-medicate may not know what dose they are taking. Moreover, opioid-naïve people (including children) who ingest methadone can die of methadone intoxication.

OTPs must assess patients' adherence to responsible take-home-dose handling and have a diversion control plan. The plan may require that the OTP:

- **Remain open 7 days per week or arrange dosing at another clinic on days the clinic is closed** for certain patients to avoid providing take-home doses to new or unstable patients.
- **Contact patients randomly and request that they return their take-home containers** within a day or two to see whether they still have the medication in their possession or have altered the medication in any way.
- **Establish an appropriate drug testing program** with policies to prevent falsification of specimens and to respond to tests that are negative for methadone.
- **Require patients to store their take-home medication in a lockbox** to prevent theft or accidental use by children or others.

Duration of Methadone Treatment

Longer lengths of stay in methadone treatment are associated with superior treatment outcomes.[154] Leaving methadone treatment is associated with increased risk of death from overdose and other causes.[155,156] Patients should continue as long as they benefit, want to, and develop no contraindications.

RESOURCE ALERT

Guidance on Federal Take-Home Methadone Dose Regulations

For more information on federal take-home dose regulations for OTPs, see SAMHSA's *Federal Guidelines for Opioid Treatment Programs* (https://store.samhsa.gov/product/Federal-Guidelines-for-Opioid-Treatment-Programs/PEP15-FEDGUIDEOTP).

> The TIP expert panel considers arbitrary time limits on OUD treatment with methadone to be medically unwarranted and inappropriate. They pose a risk to patients and the public.

Dose Tapering and Methadone Discontinuation

Discuss risks and benefits with patients who wish to discontinue treatment. Explore their reasons for wanting to discontinue and solutions for potential barriers to treatment, which may include:

- **Logistics (e.g., travel, scheduling).** Transportation services, including publicly funded ride services, ride sharing, or peer support workers, may be available. If not, transferring patients to a closer OTP or to one with more suitable hours of operation may resolve the problem.
- **Costs.** Providers can help patients explore publicly supported treatment options or apply for insurance.
- **Side effects.** Changing the dose or treating side effects may resolve the problem.
- **Opinions of friends or family.** When external pressure from family or friends drives the decision, a discussion with the patient and those individuals may help.
- **A desire to switch to buprenorphine or XR-NTX treatment.** These options should be discussed.

Caution patients who are not yet stable against discontinuing treatment, because of high rates of return to illicit opioid use and increased chance of overdose death.[157] Discuss the alternative of switching to a different OUD medication. Give patients who stop treatment information about overdose prevention and encourage them to return to treatment. Prescribe naloxone to use in case of overdose.

Create a plan collaboratively with stable patients who wish to discontinue treatment that addresses:

- Gradually tapering their dose.
- Increasing psychosocial and recovery supports.
- Discontinuing dose reduction if necessary.
- Returning to medication treatment after discontinuation if they return to illicit opioid use.
- Increasing dosage if destabilization occurs.

Individualize the pace of methadone dose reduction to the patient's response. One approach is to decrease the methadone dose gradually by 5 to 10 percent every 1 to 2 weeks. Once patients reach a relatively low dose, often between 20 mg and 40 mg, they may begin to feel more craving. Some patients may choose to switch to buprenorphine for a period to complete the dose reduction. They may also wish to begin XR-NTX after an appropriate period of opioid abstinence.

Encourage patients to use techniques for preventing return to use, such as participating in recovery support groups and gaining support from counseling and family. Doing so can help patients succeed in tapering off their medication.

RESOURCE ALERT

Guidance on Opioid Overdose Prevention

For more information on preventing opioid overdose, see the *SAMHSA Opioid Overdose Prevention Toolkit* (https://store.samhsa.gov/product/Opioid-Overdose-Prevention-Toolkit/SMA18-4742).

Methadone Dosing Summary

The initial goal is to reduce opioid withdrawal and craving safely.

- Use the "start low and go slow" approach but increase dose at a rate that minimizes chances of continued illicit drug use, while monitoring for side effects.
- Increase doses gradually over several weeks.
- Assess for sedation at peak serum concentration (2–4 hours after the dose).

The eventual target is an adequate dose that:

- Stops withdrawal symptoms for 24 hours.
- Reduces or eliminates craving.
- Blunts or blocks euphoria from self-administered illicit opioids.

In general, after induction is complete, higher doses are more effective than lower doses.

Enhancing Access to OUD Medication in OTPs

Individuals on waiting lists for OTPs should receive interim methadone maintenance treatment. People on waiting lists typically continue to use illicit opioids. Many never gain admission through the waiting list process. Federal OTP regulations permit use of interim methadone maintenance to address this problem by providing methadone treatment for up to 120 days to someone on an OTP waiting list. Routine counseling and treatment planning are not required during this period.

Interim methadone maintenance has been shown to be more effective than a waiting list to facilitate entry into comprehensive methadone treatment and to reduce illicit opioid use, according to two randomized trials.[158,159] Interim methadone *requires* approval by SAMHSA and the state opioid treatment authority. For more detailed information on interim methadone maintenance, see SAMHSA's *Federal Guidelines for Opioid Treatment Programs* (https://store.samhsa.gov/product/Federal-Guidelines-for-Opioid-Treatment-Programs/PEP15-FEDGUIDEOTP).

OTPs can overcome geographic barriers by opening a medication unit of the parent OTP site. Under the aegis of a certified OTP, a medication unit may provide methadone or buprenorphine administration, dispensing capacity, and urine drug testing, but not counseling. The parent clinic must provide counseling and other required services. Such arrangements can lessen the amount of time required to drive to a parent OTP location in large states with rural populations.

SAMHSA's *Federal Guidelines for Opioid Treatment Programs* offers more information on medication units and other OTP regulations (https://store.samhsa.gov/product/Federal-Guidelines-for-Opioid-Treatment-Programs/PEP15-FEDGUIDEOTP)

Chapter 3B Appendix

Sample Standard Consent to Opioid Maintenance Treatment Form for OTPs

CONSENT TO PARTICIPATE IN METHADONE OR BUPRENORPHINE TREATMENT

Patient's Name: _____ **Date:** _____

I authorize and give voluntary consent to _____ [insert name of program] to dispense and administer medications—including methadone or buprenorphine—to treat my opioid use disorder. Treatment procedures have been explained to me, and I understand that I should take my medication at the schedule determined by the program physician, or his/her designee, in accordance with federal and state regulations.

I understand that, like all other medications, methadone or buprenorphine can be harmful if not taken as prescribed. It has been explained to me that I must safeguard these medications and not share them with anyone because they can be fatal to children and adults if taken without medical supervision.

I also understand that methadone and buprenorphine produce physical opioid dependence.

Like all medications, they may have side effects. Possible side effects, as well as alternative treatments and their risks and benefits, have been explained to me.

I understand that it is important for me to inform any medical and psychiatric provider who may treat me that I am enrolled in an opioid treatment program. In this way, the provider will be aware of all the medications I am taking, can provide the best possible care, and can avoid prescribing medications that might affect my treatment with methadone or buprenorphine or my recovery.

I understand that I may withdraw voluntarily from this treatment program and discontinue the use of these medications at any time. If I choose this option, I understand I will be offered medically supervised withdrawal.

For women of childbearing age: Pregnant women treated with methadone or sublingual or buccal buprenorphine have better outcomes than pregnant women not in treatment who continue to use opioid drugs. Newborns of mothers who are receiving methadone or buprenorphine treatment may have opioid withdrawal symptoms (i.e., neonatal abstinence syndrome). The delivery hospital may require babies who are exposed to opioids before birth to spend a number of days in the hospital for monitoring of withdrawal symptoms. Some babies may also need medication to stop withdrawal. If I am or become pregnant, I understand that I should tell the medical staff of the OTP right away so I can receive or be referred to prenatal care. I understand that there are ways to maximize the healthy course of my pregnancy while I am taking methadone or buprenorphine.

Signature of Patient: _____ **Date of Birth:** _____

Date: _____ **Witness:** _____

Adapted from material in the public domain[160]

Chapter 3C: Naltrexone

Chapter 3C gives an overview of naltrexone pharmacology and specific guidance on dosing for oral and injectable naltrexone.

The opioid receptor antagonist naltrexone was synthesized in the 1960s to block the euphoric effects of morphine.[161] Oral naltrexone was approved by the Food and Drug Administration (FDA) in 1984 for the blockade of the effects of exogenously administered opioids. Long-acting, sustained-release opioid agonist preparations have been investigated since the 1970s to improve adherence over oral medications. In 2010, FDA approved injectable extended-release naltrexone (XR-NTX) for preventing return to opioid dependence after medically supervised withdrawal.

Despite its potential advantages (e.g., no abuse liability, no special regulatory requirements), oral naltrexone is not widely used to treat opioid use disorder (OUD) because of low rates of patient acceptance, difficulty in achieving abstinence for the necessary time before initiation of treatment, and high rates of medication nonadherence.[162]

Before initiating either formulation of naltrexone, patients must be opioid abstinent for an adequate period of time after completing opioid withdrawal. Medically supervised opioid withdrawal can be conducted on an outpatient or inpatient basis. The latter is often reserved for patients with co-occurring substance use disorders (SUDs) or medical or psychiatric illness.

There are several pharmacological approaches to medically supervised withdrawal. Methadone can be used for this purpose in opioid treatment programs (OTPs) and hospital settings. Patients in opioid withdrawal typically receive an individualized dose between 20 mg and 30 mg per day, gradually reduced over 6 days or more. Buprenorphine can be used in an adequate dose to lessen withdrawal symptoms and then reduced gradually over several days or more. If an opioid agonist is used for medically supervised withdrawal, an adequate interval of time following the last dose must occur before naltrexone induction. When it is not possible to use opioid agonists, alpha-2 adrenergic agonists such as clonidine can be used off label at doses from 0.1 mg to 0.3 mg every 6 to 8 hours to treat symptoms.[163]

Formulations

Oral: Oral naltrexone is a 50 mg tablet of naltrexone hydrochloride. It was approved by FDA in 1984 for blockade of the effects of exogenously administered opioids and in 1994 for alcohol dependence treatment. A Cochrane review examined 13 randomized trials among 1,158 patients who were opioid dependent and provided counseling. They were treated with or without oral naltrexone. The review concluded that **oral naltrexone was not superior to placebo or to no medication in treatment retention or illicit opioid use reduction.**[164]

XR-NTX: In 2006, FDA approved XR-NTX as an intramuscular (IM) injection every 4 weeks or once a month for the treatment of alcohol dependence. In 2010, FDA approved XR-NTX for the prevention of return to opioid dependence following medically supervised withdrawal. XR-NTX is a suspension of 380 mg naltrexone embedded in microspheres made from a biodegradable copolymer that undergoes hydrolysis as it absorbs water. XR-NTX requires refrigeration and is supplied as a vial of dry powder along with a separate vial of an aqueous diluent, which providers combine just before use.[165]

XR-NTX is more effective than placebo[166] or no medication[167] in reducing risk of return to opioid use.[168] A multisite randomized trial in the United States started in residential treatment programs found that buprenorphine treatment was associated with lower rates of return to use during 24 weeks of postdischarge outpatient treatment compared with XR-NTX,[169] given the significant proportion of patients who did not actually receive XR-NTX because of challenges related to XR-NTX induction. The same study found no significant between-group differences in rates of return to use when data were analyzed based solely on patients who did begin assigned medications. Study findings may not generalize to outpatient settings, where naltrexone induction may be more difficult than in residential treatment settings.

One additional study merits mention. A 12-week trial was conducted in Norway with 159 participants who, at the time of random assignment to XR-NTX or buprenorphine, had completed medically supervised withdrawal or were already opioid abstinent. XR-NTX was found to be noninferior to buprenorphine in terms of treatment retention or reduction in illicit opioid use.[170]

Pharmacology

Naltrexone is a competitive mu-opioid receptor antagonist with strong receptor affinity. **Naltrexone does not activate the mu-opioid receptor and exerts no opioid effects.** Unlike opioid agonists, naltrexone will not alleviate withdrawal symptoms, will not cause withdrawal when stopped, and cannot be diverted.

If patients maintained on naltrexone use opioid agonists, naltrexone can block their effects—a key feature of its therapeutic efficacy. However, because the interaction at the receptor is competitive, the **blockade can potentially be overridden with high doses of opioids.**

Taking naltrexone after recent use of opioids can precipitate opioid withdrawal. Given its strong affinity, naltrexone can displace other opioids from the receptor. Patients must typically wait 7 to 10 days after their last use of short-acting opioids and 10 to 14 days after their last use of long-acting opioids before taking their first dose of naltrexone.

Bioavailability

Oral: The gastrointestinal tract readily absorbs oral naltrexone. Peak concentrations occur in 1 to 2 hours.[171]

XR-NTX: IM injection causes a transient peak blood concentration 2 hours after injection and another at 2 to 3 days after injection.[172] About 14 days after injection, concentrations gradually diminish, with measurable blood levels for more than 1 month.

Both formulations are extensively metabolized by the kidneys and liver, but without CYP450 enzyme system involvement. Unlike methadone and buprenorphine, **naltrexone has limited potential drug–drug interactions.** Its major metabolite, 6-beta naltrexol, is also a mu-opioid receptor antagonist. It is eliminated primarily by the kidneys in the urine.[173]

Orally administered naltrexone has a half-life of approximately 4 hours. Its primary metabolite, 6-beta-naltrexol, is a weak mu-opioid receptor antagonist with a half-life of approximately 12 hours.[174]

XR-NTX, or "depot naltrexone," is encapsulated in biodegradable polymer microspheres. **It provides opioid blockade by delivering steady naltrexone concentrations for about 1 month.[175]** Elimination half-life is 5 to 10 days. Repeated administration causes no accumulation of naltrexone or its metabolites.

Dosing Considerations

XR-NTX

XR-NTX is indicated for the prevention of return to opioid dependence following medically supervised opioid withdrawal. Appropriate patients should have an adequate period of abstinence with no signs of opioid withdrawal before XR-NTX administration. Patients must be willing to receive monthly IM injections. Become

acquainted with the FDA label for XR-NTX, which is available online (https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=cd11c435-b0f0-4bb9-ae78-60f101f3703f).

Contraindications

Contraindications to receiving XR-NTX (as well as to receiving oral naltrexone, with the exception of hypersensitivity to the XR-NTX suspension and diluent) include:[176]

- Current pain treatment with opioid analgesics.
- Current physiological opioid dependence.
- Current acute opioid withdrawal.
- Severe hepatic impairment.
- Naloxone challenge (Exhibit 3C.1) or oral naltrexone dose causing opioid withdrawal symptoms.
- Positive urine opioid screen for morphine, methadone, buprenorphine, oxycodone, fentanyl, or other opioids.
- History of hypersensitivity to naltrexone, polylactide-co-glycolide, carboxymethylcellulose, or any other components of the diluent.

Precautions and warnings

- **Discuss the risks and benefits of continuing naltrexone with patients who become pregnant while receiving naltrexone treatment and whose OUD is in remission.** Unlike methadone and buprenorphine, naltrexone has been little researched in pregnant populations.[177,178]
- **Patients are vulnerable to opioid overdose death** after completing the every-4-weeks or once-monthly dosing period, missing a dose, or stopping treatment. Trying to override opioid blockade with high opioid doses may cause overdose.
- **Patients may experience injection site reactions** including pain, tenderness, induration, swelling, erythema, bruising, or pruritus. Severe injection site reactions may occur (e.g., cellulitis, hematoma, abscess, sterile abscess, necrosis). Some cases may require surgical intervention and may result in significant scarring. (See the Chapter 3C Appendix for techniques to reduce injection site reactions.) As with any IM injection, use caution in patients with thrombocytopenia or a coagulation disorder.
- **Precipitated opioid withdrawal can occur in patients who used illicit opioids recently or switched from an opioid agonist medication.** Symptoms may be severe enough for hospitalization. To avoid precipitated withdrawal from either formulation, patients should typically stop use of short-acting opioid agonists for 7 to 10 days and long-acting agonists for 10 to 14 days.[179] There is active research on approaches to initiate XR-NTX more quickly for patients physically dependent on opioid agonists.[180]
- **Hepatitis has been associated with XR-NTX,** often in the presence of other potential causes of hepatic toxicity (e.g., alcohol liver disease, viral hepatitis). Monitor liver function tests during treatment. Stop naltrexone in the presence of acute hepatitis and severe liver disease.[181] Initiate or refer patients to treatment for hepatitis.
- **Use cautiously in patients with moderate-to-severe renal impairment,** because the medication is eliminated primarily through the kidneys.
- **Hypersensitivity reactions** can occur, including rash, urticaria, angioedema, and anaphylaxis.
- **Monitor patients with OUD for depression and suicidal ideation.** Naltrexone use has been occasionally associated with dysphoria,[182] although it's unclear whether this is a side effect of the medication or a manifestation of underlying depression or depressed mood related to OUD.[183] Monitor patients for depression, which is common with OUD.
- **If a patient needs emergency pain treatment,** regional anesthesia or nonopioid analgesics are alternatives to opioid analgesics. A patient who must have opioids for pain treatment or anesthesia requires continuous monitoring in an anesthesia care setting.

EXHIBIT 3C.1. Naloxone Challenge

Use the naloxone challenge to assess lack of physical opioid dependence. Naloxone can be administered via intravenous, subcutaneous, or IM routes to patients who report an adequate period of opioid abstinence and have a negative opioid urine test (including morphine, methadone, buprenorphine, and oxycodone). **A negative naloxone challenge does not guarantee that the patient will not experience precipitated opioid withdrawal upon naltrexone administration.**[184]

Intravenous Administration

1. Draw 0.8 mg naloxone into a sterile syringe.
2. Inject 0.2 mg naloxone intravenously.
3. Wait 30 seconds for signs and symptoms of withdrawal. If withdrawal signs/symptoms are present, stop the naloxone challenge and treat symptomatically.
4. If no withdrawal signs and symptoms are present and vital signs are stable, inject remaining naloxone (0.6 mg) and observe for 20 minutes. Check the patient's vital signs and monitor for withdrawal.
5. If withdrawal signs and symptoms are present, stop the naloxone challenge and treat symptomatically. The test can be repeated in 24 hours or the patient can be considered for opioid agonist treatment.
6. If no withdrawal signs and symptoms are present* and **oral naltrexone is the desired treatment course,** give the patient two tablets of 25 mg naltrexone (take one tablet on each of the next 2 days) and a sufficient number of 50 mg naltrexone tablets (take one 50 mg tablet daily starting on the third day) until they are able to fill their prescription for oral naltrexone. Skip to Step 8.
7. If no withdrawal signs and symptoms are present** and **XR-NTX is the desired treatment course,** administer XR-NTX in the upper outer quadrant of the buttock, following package insert directions (summarized below).
8. Instruct the patient about the risk of overdose and death if they use opioids to override the blockade.

Subcutaneous Administration

1. Inject 0.8 mg naloxone subcutaneously.
2. Wait 20 minutes while checking vital signs and observing for signs and symptoms of opioid withdrawal.
3. If withdrawal signs and symptom are present, stop the naloxone challenge and treat symptomatically. The test can be repeated in 24 hours or the patient can be considered for opioid agonist treatment.
4. If no withdrawal signs and symptoms are present, follow Step 6 (for oral naltrexone treatment) or Step 7 (for XR-NTX treatment) above.

* **Optional:** If withdrawal signs and symptoms are absent, administer 25 mg oral naltrexone and observe for 2 hours. If the patient develops opioid withdrawal, treat symptomatically. If no withdrawal signs or symptoms are present following the 25 mg naltrexone dose and oral naltrexone is the desired treatment course, give the patient one tablet of 25 mg naltrexone to take the next day and 50 mg naltrexone tablets to take daily starting the day after.

** **Optional:** If withdrawal signs and symptoms are absent, administer 25 mg oral naltrexone and observe for 2 hours. If the patient develops opioid withdrawal, treat symptomatically and do not administer XR-NTX. This step is recommended to minimize the likelihood of longer lasting precipitated withdrawal in patients given XR-NTX who took buprenorphine recently (naloxone may not displace it from opioid receptors). This step can help identify a naltrexone allergy before providing XR-NTX. If no withdrawal symptoms are present following the 25 mg naltrexone dose and XR-NTX is the desired course, administer XR-NTX as described above.

Adapted from material in the public domain.[185]

Side effects

Possible side effects of XR-NTX include (see the FDA label for a complete list https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=cd11c435-b0f0-4bb9-ae78-60f101f3703f):[186]

- Insomnia.
- Injection site pain.
- Hepatic enzyme abnormalities.
- Nasopharyngitis.

Assessment

Thorough assessment helps determine whether naltrexone treatment is appropriate for a patient. (Part 2 of this Treatment Improvement Protocol [TIP] covers screening and assessment in more detail.)

Patients who have been abstinent from short-acting opioids (including tramadol) for 7 to 10 days or long-acting opioids (e.g., methadone, buprenorphine) for 10 to 14 days can initiate naltrexone following assessment that includes:

- **Checking the state prescription drug monitoring program database.**
- **Taking 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. Confirm an adequate opioid abstinence period.
  - Establish OUD diagnosis.
  - Assess for other SUDs, including those that involve alcohol, benzodiazepines, or stimulants.
- **Conducting a physical exam.**
  - **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 not exhibit any signs of opioid withdrawal before taking the first dose of naltrexone, to avoid precipitated withdrawal.
- **Obtaining 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.
  - **Conduct a pregnancy test.** Naltrexone is not recommended for OUD treatment in pregnancy. Refer pregnant patients to prenatal care.[187]
  - **Assess liver function.** Obtain liver function tests followed by periodic monitoring at 6- or 12-month intervals during treatment.[188]
  - **Obtain kidney function tests** (e.g., creatinine) for people who inject drugs.

RESOURCE ALERT

Opioid Withdrawal Scales

The COWS and other opioid withdrawal scales from Annex 10 of the World Health Organization's *Guidelines for the Psychosocially Assisted Pharmacological Treatment of Opioid Dependence* can be downloaded 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).

- **Conduct hepatitis and HIV tests.** Hepatitis B and C are common among patients entering naltrexone treatment. HIV infection is also prevalent. Everyone ages 15 to 65 should be tested at least once for HIV. Persons at higher risk, such as people who use drugs by injection, should be tested annually.[189] Anyone who is injecting or has ever injected drugs, even once, no matter how long ago, should be tested for hepatitis C, regardless of their intention to seek treatment for SUD.[190] The Centers for Disease Control and Prevention recommends hepatitis B vaccine for individuals seeking treatment for SUDs.[191]

During assessment, discuss with patients the risks and benefits of naltrexone and alternative treatment approaches. Explore patients' motivation to initiate medication treatment and to adhere to the dosing regimen. Start naltrexone if the patient:

- Meets *Diagnostic and Statistical Manual of Mental Disorders,* Fifth Edition, criteria for OUD.
- Understands risks and benefits.
- Reports opioid abstinence for 7 to 10 days (short acting) or 10 to 14 days (long acting).
- Reports no allergies to naltrexone or the components of the XR-NTX preparation.
- Does not have a coagulation disorder.
- Will not soon require opioid analgesia.
- Has a negative pregnancy test.
- Has a negative urine opioid screen for morphine, methadone, buprenorphine, oxycodone, and other opioids.
- Is free of current opioid withdrawal signs and symptoms (Exhibit 3C.2).
- Has liver function test results that do not indicate acute hepatitis or liver failure.
- Has a negative naloxone challenge result (Exhibit 3C.1).

Patient selection

No evidence clearly predicts which patients are best treated with XR-NTX versus other OUD medications. A secondary analysis of the data from a randomized trial of XR-NTX versus placebo conducted in Russia found no significant baseline predictors of successes among the 25 variables examined, including demographics, clinical severity, level of functioning, craving, and HIV serostatus.[192]

Inform patients of all their treatment options and the settings in which they are available. OTPs may be best for patients needing more structure. Tailor decisions about which medication to use to patients' medical and substance use histories, patient preferences, and treatment availability.

Pregnant women are not appropriate candidates for XR-NTX treatment.

Consider for XR-NTX treatment patients who:[193]

- **Do not wish to take opioid agonists.**
- **Have been opioid abstinent for at least 1 week,** have recently been or will soon be released from controlled environments (e.g., incarceration, residential addiction treatment), and do not wish to initiate (or are not able to access) opioid agonist treatment. For patients requesting opioid agonist treatment, methadone or buprenorphine must be started at much lower doses and increased much more slowly than for opioid-tolerant patients (see sections on methadone and buprenorphine dosing).

EXHIBIT 3C.2. Signs and Symptoms of Opioid Withdrawal

Signs	Symptoms
Runny nose	Skin crawling
Tearing	Abdominal cramps
Yawning	Temperature changes
Sweating	Nausea
Tremor	Vomiting
Vomiting	Diarrhea
Piloerection	Bone or muscle pain
Pupillary dilation	Dysphoria
	Craving for opioids

- **Have not responded well to prior adequate treatment** with opioid agonist therapy.[194]
- **Are part of an overall program with external monitoring** and significant, immediate external consequences for lack of adherence. These patients (e.g., healthcare professionals, pilots, probationers, parolees) may show higher rates of retention with XR-NTX because of required external monitoring.[195]
- **Have home locations or work schedules making daily or almost-daily OTP visits impossible or risky (e.g., job loss).**

Informed consent

Inform all patients of the following basic information:

- Their OUD diagnosis and the nature of the disorder
- Risks and benefits of XR-NTX and other OUD medications
- Risks and benefits of nonmedication treatments

Consider asking patients to sign a treatment agreement form before starting treatment. (See Appendix 3C for a sample treatment agreement.) Document informed consent discussions in the medical record.

Educate patients and their families about what to expect from naltrexone treatment (Exhibit 3C.3). A naltrexone medication guide should be dispensed to patients with each injection. Caution them about increased risk of overdose if they stop treatment and return to illicit opioid use or attempt to override the receptor blockade of XR-NTX. Document education in the medical record. Chapter 3C Appendix has a patient education counseling tool for XR-NTX.

> **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.**

Initiating XR-NTX treatment

Storage and preparation

A pharmacy will send XR-NTX and its diluent in a refrigerated package with two sets of administration needles (1.5 and 2 inches), a 1-inch preparation needle, and a needle protection device.

The XR-NTX microspheres are temperature sensitive. When the carton arrives from the pharmacy, store it in a refrigerator at 36 to 46 degrees Fahrenheit (2 to 8 degrees Celsius). The refrigerator should have a working thermometer; check the temperature regularly.

Do not freeze the carton or expose it to temperatures above 77 degrees Fahrenheit (25 degrees Celsius). XR-NTX can be stored unrefrigerated for up to 7 days before administration.

Before preparing XR-NTX for administration, keep it at room temperature for about 45 minutes. Examine the microspheres and diluent to ensure that no particulate matter or discoloration are present. Mix following FDA-approved package insert directions, using the 1-inch preparation needle. Resulting suspension should be milky white, without clumps, and able to move freely down the wall of the vial.

Two sets of needles of two different lengths are shipped with the medication in case the first needle clogs before injection. **Use the 1.5-inch needle for lean patients and the 2-inch needle for patients with more subcutaneous tissue** overlying the gluteal muscle. The longer needle helps ensure that the injection reaches the muscle. Inject patients with average body habitus with either needle.

Administration

Administer XR-NTX every 4 weeks or once a month as a 380 mg IM gluteal injection. Alternate buttocks for each 4-week injection. Given the risk of severe injection site reactions, FDA requires a risk evaluation and mitigation strategy (www.vivitrolrems.com) for XR-NTX including a patient counseling tool, a patient medication guide, and a visual aid to reinforce proper XR-NTX injection technique.

EXHIBIT 3C.3. Key Points of Patient Education for Naltrexone

- Do not use any opioids in the 7 to 10 days (for short acting) or 10 to 14 days (for long acting) before starting XR-NTX, to avoid potentially serious opioid withdrawal symptoms. Opioids include:
  - Heroin.
  - Prescription opioid analgesics (including tramadol).
  - Cough, diarrhea, or other medications that contain codeine or other opioids.
  - Methadone.
  - Buprenorphine.
- Seek immediate medical help if symptoms of allergic reaction or anaphylaxis occur, such as:
  - Itching.
  - Swelling.
  - Hives.
  - Shortness of breath.
  - Throat tightness.
- Do not try to override the opioid blockade with large amounts of opioids, which could result in overdose.
- Understand the risk of overdose from using opioids near the time of the next injection, after missing a dose, or after stopping medications.
- Report injection site reactions including:
  - Pain.
  - Hardening.
  - Lumps.
  - Blisters.
  - Blackening.
  - Scabs.
  - An open wound.

  Some of these reactions could require surgery to repair (rarely).
- Report signs and symptoms of hepatitis (e.g., fatigue, abdominal pain, yellowing skin or eyes, dark urine).
- Report depression or suicidal thoughts. Seek immediate medical attention if these symptoms appear.
- Seek medical help if symptoms of pneumonia appear (e.g., shortness of breath, fever).
- Inform providers of naltrexone treatment, as treatment differs for various types of pneumonia.
- Inform all healthcare professionals of XR-NTX treatment.
- Report pregnancy.
- Inform providers of any upcoming medical procedures that may require pain medication.
- Understand that taking naltrexone may result in difficulty achieving adequate pain control if acute medical illness or trauma causes severe acute pain.
- Wear medical alert jewelry and carry a medical alert card indicating you are taking XR-NTX. A patient wallet card or medical alert bracelet can be ordered at 1-800-848-4876.

Follow-up care after first dose

Examine patients within a week of administering their first XR-NTX dose. It can be clinically beneficial to maintain weekly contact in the first month to:

- Provide supportive counseling.
- Assess ongoing drug or alcohol use.
- Monitor side effects.
- Obtain drug testing.
- Follow up on status of referrals to counseling or other services.

Patients who test the opioid blockade of XR-NTX may discontinue use because of the blocking of the euphoric effects of illicit opioids.[196] Patients who miss a dose can restart medication (use procedures outlined earlier in this section) after an adequate period of opioid abstinence (7 to 14 days).

> **The TIP expert panel cautions that, based on current data, arbitrary time limits on XR-NTX are inappropriate.**

See Chapter 3E for information on the management of patients taking naltrexone in office-based treatment settings.

Duration of treatment

Barring contraindications, patients should continue taking XR-NTX as long as they benefit from it and want to continue. Data are limited on the long-term effectiveness of XR-NTX compared with methadone or buprenorphine.

Treatment discontinuation

When patients wish to discontinue naltrexone, engage in shared decision making and explore:

- Their reasons for wanting to discontinue.
- The risks and benefits of discontinuing.
- Problem-solving strategies that can help them make an informed choice.
- Their appropriateness for buprenorphine or methadone treatment.

Discourage patients who are not yet stable from discontinuing treatment, because of the high rate of return to illicit opioid use and the increased chance of overdose death.

Signs that a patient may be ready to discontinue medication include:[197]

- Sustaining illicit drug abstinence over time.
- Having stable housing and income.
- Having no legal problems.
- Having substantially reduced craving.
- Attending counseling or mutual-help groups.

Patients who discontinue should have a recovery plan that may include monitoring as well as adjunctive counseling and recovery support. If they return to opioid use, encourage them to return for assessment and reentry into treatment.

Given the high risk of return to illicit opioid use, **offer patients information about opioid overdose prevention and a naloxone prescription they can use in case of overdose.** When patients stop using naltrexone, they will have no tolerance for opioids. Their risk of overdose is very high if they use again. For more information, see the *SAMHSA Opioid Overdose Prevention Toolkit* (https://store.samhsa.gov/product/Opioid-Overdose-Prevention-Toolkit/SMA18-4742).

Rapid naltrexone induction

Patients with OUD need to discontinue opioids and wait 7 to 14 days after last opioid use (including any given for withdrawal treatment) before receiving XR-NTX. As described above, they can do so through medically supervised withdrawal in a controlled environment, such as an inpatient unit, residential addiction treatment program, correctional facility, or hospital, or on an outpatient basis.

Financial issues and managed care constraints may influence patients' access to controlled treatment environments. The alternative—**abstaining long enough after outpatient medically supervised withdrawal—is challenging.** Thus, various approaches to rapid naltrexone induction have been developed[198] and more recently refined in research settings.[199,200,201]

Consider rapid induction in specialty addiction treatment programs, not general medical settings. It may be hard for providers in general medical settings to start XR-NTX successfully with patients who need medically supervised opioid withdrawal. Rapid induction approaches are likely beyond the scope of general outpatient

RESOURCE ALERT

Patient and Family Educational Resources

Decisions in Recovery: Treatment for Opioid Use Disorder offers information for patients on the use of medications for OUD (https://store.samhsa.gov/product/SMA16-4993)

Medication-Assisted Treatment for Opioid Addiction: Facts for Families and Friends offers information for family and friends (https://mha.ohio.gov/Portals/0/assets/HealthProfessionals/About%20MH%20and%20Addiction%2Treatment/MAT/SMA14-4443.pdf?ver=2018-11-26-113004-157)

settings. However, patients can successfully initiate XR-NTX in a general outpatient medical setting if they:

- Have been abstinent for sufficient time and pass the naloxone challenge.
- Started taking XR-NTX elsewhere and are due for the next injection.

One randomized trial compared two approaches to starting XR-NTX on an outpatient basis. This study assigned adults dependent on opioids to either a standard 14-day buprenorphine-assisted opioid withdrawal or more rapid 7-day oral naltrexone-assisted opioid withdrawal.[202] Naltrexone-assisted withdrawal was conducted over 7 days. It included 1 day of buprenorphine administration; 1 day with ancillary medications including clonidine and clonazepam but no buprenorphine; followed by 4 days of ancillary medications and increasing daily doses of oral naltrexone (starting with 1 mg, 3 mg, 12 mg, and 25 mg); and concluding on day 7 with XR-NTX administration. Buprenorphine-assisted withdrawal consisted of a 7-day buprenorphine taper followed by the recommended 7 days without opioids. The naltrexone-assisted withdrawal group was significantly more likely to begin XR-NTX compared with the buprenorphine-assisted withdrawal group (56.1 percent versus 32.7 percent, respectively). This type of approach, which must be conducted with careful daily monitoring, is used in some residential programs and may prove to be a useful approach to outpatient XR-NTX induction in specialty programs. More discussion on rapid induction approaches is available in *Implementing Antagonist-Based Relapse Prevention Treatment for Buprenorphine-Treated Individuals,*[203] available online (http://pcssmat.org/wp-content/uploads/2015/02/PCSSMAT-Implementing-Antagonist-with-Case.Bisaga.CME_.pdf).

Oral Naltrexone

The effectiveness of oral naltrexone is limited, given poor adherence and the requirement of 7 to 14 days of opioid abstinence before initiation. During this waiting period, patients may drop out of care. One study found significantly lower patient retention in treatment after incarceration for patients treated with oral naltrexone compared with methadone.[204]

Oral naltrexone blocks opioid-induced euphoria for only a day or two. When patients stop taking it, risks of return to opioid use and overdose increase.

The TIP expert panel doesn't recommend using oral naltrexone except in the limited circumstances described in the following sections. This view is in keeping with expert reviews for the United Kingdom's National Health Service,[205] a clinical practice guideline published by the Department of Veterans Affairs and Department of Defense,[206] and a Cochrane review.[207]

Indications and contraindications, precautions and warnings, side effects, and assessment.

All are similar to those for XR-NTX, save issues specific to suspension/diluent contents and the injection itself.

Patient Selection

In limited circumstances, oral naltrexone may be considered after the risks and benefits, as well as alternative treatments, are discussed with the patient. Examples include:

- **Patients who cannot afford XR-NTX** but wish to take an opioid receptor antagonist.
- **Patients with high levels of monitoring and negative consequences for nonadherence,** such as healthcare professionals who may not be permitted to have opioid agonist treatment.[208,209]

> **The TIP expert panel does not recommend that payers require patients to fail oral naltrexone before providing access to XR-NTX, given the risk of unintentional overdose death if the patient returns to illicit opioid use.**

- **Patients leaving controlled environments** (e.g., prisons, hospitals, inpatient addiction rehabilitation) who may benefit from medication to prevent return to illicit drug use but cannot or will not take XR-NTX and do not wish to be treated with (or do not have access to) opioid agonists.

Patients who have taken methadone or extensively used heroin are especially poor oral naltrexone candidates.[210]

Dosing

Following a negative naloxone challenge, the first oral dose of naltrexone can be 25 mg (half of the usual daily naltrexone maintenance dose). This reduces risk of a more severe precipitated opioid withdrawal than could occur with a full 50 mg dose. This lower dose may also reduce nausea associated with the first naltrexone dose. The dose can be increased to 50 mg daily on the second day.

To increase adherence, arrange for directly observed administration of oral naltrexone. This is more feasible if patients who tolerate a daily dose of 50 mg are switched to a 3-days-per-week regimen for a total weekly dose of 350 mg (e.g., administer 100 mg on Monday and Wednesday and 150 mg on Friday). A member of the patient's social network (e.g., spouse) may also directly observe therapy.

Duration of treatment

The optimal length of treatment with oral naltrexone is not known. In general, the longer patients take an effective medication, the better their outcomes.

Use of illicit opioids during treatment with oral naltrexone is a cause of concern and may be a precursor to treatment discontinuation.[211] Some patients will initially test the opioid blockade with illicit opioids and then discontinue opioid use. However, others will continue using illicit opioids.[212]

If patients continue to test the blockade, immediately discuss alternative treatment plans that include:

- Increased counseling.
- Switching to XR-NTX.
- Closer monitoring.
- Directly observed oral naltrexone therapy.
- Residential treatment.
- Assessment for the appropriateness of buprenorphine or methadone.

Naltrexone Dosing Summary

XR-NTX

- Before administering XR-NTX, keep it at room temperature for about 45 minutes.
- Use the correct needle length to ensure the injection is in the gluteal muscle.
  - Use the 2-inch needle for patients with more subcutaneous tissue and the 1.5-inch needle for patients with less adipose tissue.
  - Use either length in patients with normal body habitus.
- Use proper aseptic technique.
- Use proper gluteal IM injection technique.
- Never inject intravenously or subcutaneously.
- Repeat the injection every 4 weeks or once per month.

Oral Naltrexone

- Use in limited circumstances after discussing risks and benefits, as well as alternative treatment options, with the patient.
- Do the naloxone challenge.
- The first oral naltrexone dose should be 25 mg.
- The dose can be increased on the second day to 50 mg daily if necessary.
- If desired, switch patients who tolerate a daily dose of 50 mg to a 3-days-per-week regimen for a total weekly dose of 350 mg.

Chapter 3C Appendix

Sample XR-NTX 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 agreement for extended-release injectable naltrexone office-based opioid use disorder treatment:

1. The risks and benefits of extended-release injectable naltrexone treatment have been explained to me.
2. The risks and benefits of other treatment for opioid use disorder (including methadone, buprenorphine, and nonmedication treatments) have been explained to me.
3. I will be on time to my appointments and respectful to the office staff and other patients.
4. I will keep my healthcare provider informed of all my medications (including herbs and vitamins) and medical problems.
5. I agree not to obtain or take prescription opioid medications prescribed by any other healthcare provider without consultation from my naltrexone prescriber.
6. 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.
7. If I miss a scheduled appointment for my next extended-release naltrexone injection, I understand that I should reschedule the appointment as soon as possible because it is important to receive the medication on time to reduce the risk of opioid overdose should I return to use.
8. If I come to the office intoxicated, I understand that my healthcare provider will not see me.
9. Violence, threatening language or behavior, or participation in any illegal activity at the office will result in treatment termination from the clinic.
10. 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.
11. I understand that initially I will have weekly office visits until my condition is stable.
12. 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.
13. I may be seen less than every 2 weeks based on goals made by my healthcare provider and me.
14. I understand that people have died trying to overcome the naltrexone opioid blockade by taking large amounts of opioids.
15. I understand that treatment of opioid use disorder involves more than just taking medication. I agree to follow my healthcare provider's recommendations for additional counseling and/or for help with other problems.
16. I understand that there is no fixed time for being on naltrexone and that the goal of treatment is for me to stop using all illicit drugs and become successful in all aspects of my life.
17. I understand that my risk of overdose increases if I go back to using opioids after stopping naltrexone.
18. I have been educated about the other two FDA-approved medications used to treat opioid use disorder, methadone and buprenorphine, and I prefer to receive treatment with naltrexone.
19. I have been educated about the increased chance of pregnancy when stopping illicit opioid use and starting naltrexone treatment and have been informed about methods for preventing pregnancy.
20. I have been informed that if I become pregnant during naltrexone treatment, I should inform my provider and have a discussion about the risks and benefits of continuing to take naltrexone.

Other specific items unique to my treatment include:

Patient's Name (print): _____

Patient's Signature: _____ Date: _____

This form is adapted from the American Society of Addiction Medicine's Sample Treatment Agreement, which is updated periodically; the 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.[213]

Patient Counseling Tool for XR-NTX

Patient Counseling Tool
VIVITROL® (naltrexone for extended-release injectable suspension)

Risk of sudden opioid withdrawal during initiation and re-initiation of VIVITROL
Using any type of opioid including street drugs, prescription pain medicines, cough, cold or diarrhea medicines that contain opioids, or opioid dependence treatments buprenorphine or methadone, in the 7 to 14 days before starting VIVITROL may cause severe and potentially dangerous sudden opioid withdrawal.

Risk of opioid overdose
Patients may be more sensitive to the effects of lower amounts of opioids:

- After stopping opioids (detoxification)
- When the next VIVITROL dose is due
- If a dose of VIVITROL is missed
- After VIVITROL treatment stops

Patients should tell their family and people close to them about the increased sensitivity to opioids and the risk of overdose even when using lower doses of opioids or amounts that they used before treatment. Using large amounts of opioids, such as prescription pain pills or heroin, to overcome effects of VIVITROL can lead to serious injury, coma, and death.

Risk of severe reactions at the injection site
Remind patients of these **possible** symptoms at the **injection site:**

- Intense pain
- The area feels hard
- Large areas of swelling
- Lumps
- Blisters
- Open wound
- Dark scab

Some of these injection site reactions have required surgery.
Tell your patients to contact a healthcare provider if they have any reactions at the injection site.

Risk of liver injury, including liver damage or hepatitis
Remind patients of the possible symptoms of liver damage or hepatitis.

- Stomach area pain lasting more than a few days
- Dark urine
- Yellowing of the whites of eyes
- Tiredness

Patients may not feel the therapeutic effects of opioid-containing medicines for pain, cough or cold, or diarrhea while taking VIVITROL.

Patients should carry written information with them at all times to alert healthcare providers that they are taking VIVITROL, so they can be treated properly in an emergency.

A Patient Wallet Card or Medical Alert Bracelet can be ordered from: 1-800-848-4876, Option #1.

PLEASE SEE PRESCRIBING INFORMATION AND MEDICATION GUIDE.

Alkermes®

www.vivitrol.com

Vivitrol®
(naltrexone for extended-release injectable suspension)

Available online (www.vivitrolrems.com/content/pdf/patinfo-counseling-tool.pdf).
Reprinted with permission.[214]

Key Techniques for Reducing Injection Site Reactions[215]

To reduce severe injection site reactions when administering XR-NTX via intramuscular injection, use the following techniques:

- **Use one of the administration needles provided with the XR-NTX kit to ensure that the injection reaches the gluteal muscle.** Use the 2-inch needle for patients who have more subcutaneous adipose tissue. Use the 1.5-inch needle for patients with less subcutaneous adipose tissue. Either needle is appropriate for use with patients who have average amounts of subcutaneous adipose tissue.
- **Use aseptic technique when administering intramuscularly.** Using a circular motion, clean the injection site with an alcohol swab. Let the area dry before administering the injection. Do not touch this area again before administration.
- **Use proper deep intramuscular injection technique into the gluteal muscle.** XR-NTX must not be injected intravenously, subcutaneously, or into adipose tissue. Accidental subcutaneous injection may increase the risk of severe injection site reactions.
  - **Administer the suspension by deep intramuscular injection into the upper outer quadrant of gluteal muscle,** alternating buttocks per monthly injection.
  - **Remember to aspirate for blood before injection.** If blood aspirates or the needle clogs, do not inject. Change to the spare needle provided in the package and administer into an adjacent site in the same gluteal region, again aspirating for blood before injection.
  - **Inject the suspension in a smooth, continuous motion.**

A patient counseling tool is available to help you counsel your patients before administration about the serious risks associated with XR-NTX.

The above information is a selection of key safety information about the XR-NTX injection. For complete safety information, refer to the directions for use and the prescribing information provided in the medication kit. You can also obtain this information online (www.vivitrolrems.com) or by calling 1-800-VIVITROL.

Available online (www.vivitrolrems.com/content/pdf/patinfo-injection-poster.pdf).

Chapter 3D: Buprenorphine

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

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.[216,217,218] 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.[219,220,221,222,223] Buprenorphine is on the World Health Organization (WHO) list of essential medications.[224]

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.[225]

Formulations

History of Approvals

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

- 2002: Sublingual buprenorphine/naloxone sublingual tablets (Suboxone); sublingual buprenorphine tablets (Subutex). The manufacturer discontinued the tablet formulations of both from the U.S. market after the film's approval, but generic tablet formulations are still available (Exhibit 3A.5, Chapter 3A).
- 2010: Buprenorphine/naloxone sublingual films.
- 2013: Buprenorphine/naloxone sublingual tablets (Zubsolv).[226]
- 2014: Buprenorphine/naloxone buccal films (Bunavail).[227]
- 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.

> **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.

Exhibit 3D.1 lists product strengths and recommended once-daily maintenance doses. For simplicity, dosing information here refers to sublingual Suboxone or generic equivalents. An 8 mg/2 mg dosage 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.

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 Suboxone or generic 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

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[228] • 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[229,230] • Buprenorphine hydrochloride • Naloxone hydrochloride	Sublingual tablet, film	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[231,232] • Buprenorphine hydrochloride	Sublingual tablet	2 mg 8 mg	**Target:** 16 mg **Range:** 4 mg to 24 mg*
Suboxone[233,234] • 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[235,236] • 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.[237,238]

Adapted from material in the public domain.[239]

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.[240]

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.[241,242,243]

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.[244] 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[245] with a mean half-life of 24 to 42 hours.[246] It dissociates slowly from the receptor.

Buprenorphine can be safely dosed (even at double the *stabilized* dose) less than daily.[247] 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 bioavailability 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.[248,249]

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.[250]

Metabolism and Excretion

Buprenorphine:[251,252]

- 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,[253] 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.5 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.[254]

Precautions and Warnings

- **Respiratory depression and overdoses are uncommon in adults, but they do happen.[255]** Most fatal overdoses involve IV buprenorphine misuse or concurrent central nervous system depressant use, including high doses of benzodiazepines, alcohol, or other

sedatives.[256,257] However, fatal overdoses have been reported in opioid-naïve patients treated with 2 mg buprenorphine for pain.[258] Exhibit 3D.2 summarizes the management of patients with preexisting respiratory impairment.

- **Unintentional pediatric exposure can be life threatening or fatal.[259]** 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.[260] Exhibit 3D.2 summarizes management of patients with hepatic impairment.

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

CONTRAINDICATION/CAUTION	MANAGEMENT
Compromised respiratory function For example, 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.[263] • 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.[261,262]	• Mild impairment (Child-Pugh score of 5–6):[264] No dose adjustment needed. • Moderate impairment (Child-Pugh score of 7–9):[265] 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;[266,267] monitor for signs and symptoms of buprenorphine toxicity or overdose.[268] Naloxone may interfere with buprenorphine's efficacy.[269,270] • Severe impairment (Child-Pugh score of 10–15):[271] Do not use the combination product.[272] 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.[273]

*Moderate-to-severe impairment results in much more reduced clearance of naloxone than of buprenorphine. Nasser et al.[274] 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.[275]

- **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.[276,277]
- 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.[278]
- **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.[279]
- **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.[280] 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.[281] 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.[282]
  - Dose of buprenorphine administered. The smaller the dose of buprenorphine, the less likely it is to precipitate withdrawal.[283,284]
- **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.[285,286,287] 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.[288] Monitoring is still needed for patients who are starting or stopping medications that are CYP450 3A4 enzyme inhibitors or inducers or that compete with buprenorphine for this enzyme. A previously therapeutic and stable dose of either buprenorphine or the coadministered medication may be altered when one of these medications is started or stopped. In the case of buprenorphine, oversedation or withdrawal symptoms may result. In the case of altered levels of other pharmacotherapies, the patient may experience a lack of therapeutic benefit or toxic side effects of that drug. Special attention should be paid to patients using or starting depot formulations of buprenorphine. Prior to initiating a depot formulation, talk with the patient about waiting until any time-limited therapy with a potential inhibitor, inducer, or substrate of CYP450 3A4 is complete, and ensure that adherence to any such medications needed chronically is good. Make sure the patient fully understands the possible risk of fluctuations in buprenorphine serum levels resulting in sedation or withdrawal symptoms and if compliance with an inhibitor, inducer, or substrate of CYP450 3A4 is erratic. If an inhibitor, inducer, or substrate of CYP450 3A4 is to be started or stopped for a patient stable on a depot formulation of buprenorphine, the patient should be monitored closely for oversedation or signs of withdrawal. Remember, signs and symptoms may not appear until the new medication approaches a therapeutic blood level. Signs of withdrawal may be relieved, if necessary, with the short-term use of additional low doses of transmucosal buprenorphine. Patients who experience sedation may need to take safety precautions with some activities. In severe cases, removal of the depot formulation, if possible, may need to be considered. **Exhibit 3D.3 partially lists these**

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

Drugs that may DECREASE buprenorphine serum levels	
Drug	**Mechanism**
Anticonvulsants	
Phenobarbital, phenytoin, primidone, carbamazepine	Induces cytochrome P450 3A4
Antibiotics	
Rifampin	Induces cytochrome P450 3A4
Immune Suppressants	
Dexamethasone	Induces cytochrome P450 3A4
Drugs that may INCREASE buprenorphine serum levels	
Drug	**Mechanism**
Antibiotics	
Clarithromycin	Inhibits cytochrome P450 3A4
Clindamycin, dapsone, erythromycin	Competes with buprenorphine for cytochrome P450 3A4 enzyme
Antidepressants	
Fluoxetine, fluvoxamine, nefazodone	Inhibits cytochrome P450 3A4

Continued on next page

EXHIBIT 3D.3. Partial List of Medications Metabolized by Cytochrome P450 3A4 (continued)

Drugs that may INCREASE buprenorphine serum levels	
DRUG	**MECHANISM**
Antifungals	
Fluconazole, itraconazole, miconazole	Inhibits cytochrome P450 3A4
Ketoconazole	Inhibits and competes with buprenorphine for cytochrome P450 3A4
Antihypertensives	
Nicardipine, verapamil	Inhibits cytochrome P450 3A4
Amlodipine, diltiazem, felodipine, nifedipine, nimodipine	Competes with buprenorphine for cytochrome P450 3A4 enzyme
Antiarrhythmics	
Amiodarone	Inhibits cytochrome P450 3A4
Disopyramide, quinidine	Competes with buprenorphine for cytochrome P450 3A4 enzyme
Hormones	
Estrogen, oral contraceptives, progestins	Competes with buprenorphine for cytochrome P450 3A4 enzyme
Sedative/Hypnotics	
Alprazolam, clonazepam, diazepam, midazolam	Competes with buprenorphine for cytochrome P450 3A4 enzyme
Immune Suppressants	
Cyclosporine, zafirlukast	Inhibits cytochrome P450 3A4
Statins	
Atorvastatin, lovastatin, simvastatin	Competes with buprenorphine for cytochrome P450 3A4 enzyme
Gastric Agents	
Aprepitant, cimetidine	Inhibits cytochrome P450 3A4
Analgesics	
Fentanyl	Competes with buprenorphine for cytochrome P450 3A4 enzyme
Antihistamines	
Loratadine	Competes with buprenorphine for cytochrome P450 3A4 enzyme
Chemotherapeutics	
Doxorubicin, etoposide, ifosfamide, paclitaxel, vinblastine	Competes with buprenorphine for cytochrome P450 3A4 enzyme
Blood Thinners	
Warfarin	Competes with buprenorphine for cytochrome P450 3A4 enzyme

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.[289]

medications, including some anticonvulsants, and antibiotics, and Exhibit 3D.4 lists 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.[290]

Combination antiretroviral therapy (atazanavir/ritonavir) increases buprenorphine and norbuprenorphine serum concentrations.[291] Case reports have demonstrated signs of buprenorphine excess (sedation). Decreasing buprenorphine can improve this symptom.[292]

Other research has demonstrated no need to adjust the buprenorphine dose among patients taking atazanavir.[293]

For tuberculosis treatment, rifampin but not rifabutin may decrease buprenorphine concentrations. Rifampin produced opioid withdrawal in 50 percent of research volunteers with opioid dependence.[294]

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.

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

MEDICATION	TYPE	POTENTIAL INTERACTION
Atazanavir	Protease inhibitor	Increased buprenorphine concentrations. May cause cognitive impairment[295,296] or oversedation.[297,298] Slower titration or dose reduction of buprenorphine may be warranted.[299,300]
Darunavir-ritonavir	Protease inhibitor	Some pharmacokinetic (PK) effect; dose adjustments unlikely to be needed, but clinical monitoring is recommended.[301]
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.[302,303]
Efavirenz	Nonnucleoside reverse transcriptase inhibitor	Some PK effect; dose adjustments unlikely to be needed.[304]
Elvitegravir (with cobicistat)	Integrase inhibitor	Some PK effect; no dose adjustments needed.[305]
Nevirapine	Nonnucleoside reverse transcriptase inhibitor	Some PK effect; no dose adjustments needed.[306]
Ritonavir	Protease inhibitor	Some PK effect; no dose adjustments needed.[307]
Tipranavir	Protease inhibitor	Some PK effect; no dose adjustments needed.[308]

Adapted from material in the public domain.[309]

Serotonin syndrome can occur with simultaneous opioid and antidepressant treatment. There are only a few case reports of serotonin syndrome with buprenorphine,[310] 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 be 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 is recommended for OUD in pregnancy.[311] 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.[312] 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.[313,314] 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.**

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).

- **Conduct hepatitis and HIV tests.** Hepatitis B and C are common among patients entering buprenorphine treatment. HIV infection is also prevalent. Everyone ages 15 to 65 should be tested at least once for HIV. Persons at higher risk, such as people who use drugs by injection, should be tested annually.[315] Anyone who is injecting or has ever injected drugs, even once, no matter how long ago, should be tested for hepatitis C, regardless of their intention to seek treatment for SUD.[316] The Centers for Disease Control and Prevention recommends hepatitis B vaccination for individuals seeking treatment for SUDs.[317]

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 or Referral" 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,[318] and it's often used to self-treat opioid withdrawal rather than to "get high."[319,320]

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.

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

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.[321] There is no absolute definition of clinical stability, but per the implant package insert, patients may be stable if they are:[322]

- 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.

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

> 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.
  - Dizziness.
  - Nausea.
  - Vomiting.
  - Sweating.
  - Constipation.
  - Sexual dysfunction.
- 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* (https://mha.ohio.gov/Portals/0/assets/HealthProfessionals/About%20MH%20and%20Addiction%20Treatment/MAT/SMA14-4443.pdf?ver=2018-11-26-113004-157)

prescriber (or, for home induction, that meets predefined self-assessment criteria) to avoid precipitated withdrawal.

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.[323] However, office-based induction can be a barrier to treatment initiation. Home induction is increasingly common.[324]

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.[325] Retention rates are similar to office inductions,[326] 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.[327,328] 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.

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.)

> **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.

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.[329] 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.[330] 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.[331] 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.[332] 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.[333] 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.[334] 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.[335] 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.

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.

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.[336]
  - 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.**

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.[337] 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[338] 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,[339,340] the safety data are insufficient at this time to recommend its use.[341] 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.[342]
- 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 (https://probuphinerems.com/).

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,[343] 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.[344]

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

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

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

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.[345] 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.[346] 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 members and others in the patient's recovery support network.
  - See the *SAMHSA Opioid Overdose Prevention Toolkit* (https://store.samhsa.gov/product/Opioid-Overdose-Prevention-Toolkit/SMA18-4742) 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.[347,348,349]

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).[350]

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	

1

Continued on next page

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	

2

Available online (www.accessdata.fda.gov/drugsatfda_docs/rems/BTOD_2017-01-23_Appropriate_Use_Checklist.pdf).
Reprinted from material in the public domain.[351]

Sample Goal Sheet and Coping Strategies Form

Patient's Name: _____ **Date:** _____

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.

Sample Goal-Setting Form

Patient's 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.

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.
- 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).

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

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 _____].
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).

Continued on next page

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's Name (print): _____

Patient's Signature: _____ Date: _____

This form is adapted from the American Society of Addiction Medicine's Sample Treatment Agreement, which is updated periodically; the most current version of the agreement is available online (https://www.asam.org/docs/default-source/advocacy/sample-treatment-agreement30fa159472bc604ca5b7ff000030b21a.pdf?sfvrsn=bd4675c2_0).

Adapted with permission.[352]

Patient Urine Drug Screen and Medication Count Monitoring Form

Patient's Name: _____ **Date 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 first 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,

_____
Signature

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

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

Management of patients taking medications for opioid use disorder (OUD) varies by setting. Whereas OBOT stabilizes patients 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 in Exhibit 3.1 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,[353] 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).

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.[354] 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, 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.[355]

- **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.[356] Initiation of HIV and hepatitis C virus treatments do not contraindicate buprenorphine treatment.[357]

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.[358] 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 re-starting 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, 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.[359]

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/product/TIP-42-Substance-Abuse-Treatment-for-Persons-With-Co-Occurring-Disorders/SMA13-3992).

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/product/general-principles-use-pharmacological-agents-treat-individuals-co-occurring-mental).

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/product/pharmacologic-guidelines-treating-individuals-post-traumatic-stress-disorder-co-occurring).

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.[360]

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.

> **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.**

- 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 or Referral" 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.
- **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.[361] (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)[362] 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.[363]

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.[364] Monitor recovery activities to ensure that patients are accessing appropriate supports and are benefiting from them (Exhibit 3E.2).

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.

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.[365]

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."[366]

- 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 recommends that patients be seen approximately once a week until they demonstrate significant reductions in or abstinence from illicit substance use.[367] 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

> **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.**

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.

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*[368] (https://store.samhsa.gov/product/tap-32-clinical-drug-testing-primary-care/sma12-4668) and ASAM's Consensus Statement on Appropriate Use of Drug Testing in Clinical Addiction Medicine.[369]

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 waiting list 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 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.[370] 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

> **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.**

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.[371] It is 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.

Administrative Considerations

Patient Limits

Individual healthcare practitioners can prescribe buprenorphine in any medical setting, as long as they apply for and receive waivers of the special registration requirements defined in the Controlled Substances Act. Several laws and regulations contain information about which healthcare practitioners are eligible to apply for a waiver and how to qualify (https://www.samhsa.gov/medication-assisted-treatment/training-materials-resources/apply-for-practitioner-waiver). This information is summarized below.

Eligible physicians, nurse practitioners, physician assistants, and other qualifying practitioners (clinical nurse specialists, certified registered nurse anesthetists, and certified nurse midwives) can apply for a waiver.

At present, clinical nurse specialists, certified registered nurse anesthetists, and certified nurse midwives are only eligible to apply for a waiver until October 1, 2023.

For the first year of waiver use, **all providers** can treat up to 30 patients at one time. However, providers who satisfy additional practice and reporting requirements, and physicians who are board certified in addiction psychiatry or addiction medicine, may request to treat up to 100 patients at a time in the first year of waiver use. Additionally, practitioners who provide MAT in "qualified practice settings," as defined in title 42, section 8.615 of the Code of Federal Regulations, may also request to treat up to 100 patients within the first year.

After the first year of waiver use, **all providers** may request to increase their patient limit to 100.

Physicians who are board certified in addiction psychiatry or addiction medicine or who satisfy additional practice and reporting requirements may apply to increase their patient limit to 275 after a year at the 100-patient limit.

Diversion Control Policies for OBOT With Buprenorphine

Controlled substance diversion refers to unauthorized provision of medication to someone for whom it was not prescribed.[372] **Patients may divert buprenorphine for various reasons, such as:**

- To "help" someone who needs medically supervised withdrawal or awaits treatment.[373,374]
- To provide income for the seller.
- To enable someone else to experience the euphoric effect of the medication.[375]

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).[376]
  - Discuss patients' plans to safely store buprenorphine. Advise patients to keep the medication in the original packaging and out of the reach of children.[377]
  - Tell patients not to store their medication 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[378] 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.[379] It should address medication storage, dispensing and administration (if applicable), and prescribing[380] (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 Drug Enforcement Administration (DEA) requirements for Drug Addiction Treatment Act of 2000 (DATA

2000)-waivered healthcare professionals is available online (https://www.deadiversion.usdoj.gov/pubs/docs/index.html).

Storage of Buprenorphine

Practices that store buprenorphine onsite must have appropriate security, which includes storing the medication in a securely locked, substantially constructed cabinet.[381] 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.

EXHIBIT 3E.3. Key Elements of an OBOT Clinic Diversion Control Plan[382]

New 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.
- Acknowledge giving or 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 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.

Ongoing Patients

Periodically check the state's PDMP.

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.

Records for Dispensers

Office-based practices that dispense buprenorphine must keep records of:[383]

- 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:

- DEA Recordkeeping Requirements for Buprenorphine Treatment (https://docs.clinicaltools.com/pdf/Buppractice/V5-Bup-How-To-Comply.pdf).

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://pcssnow.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.

> **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.

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.

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 ASAM 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 (https://pcssnow.org/education-training/).

Chapter 3E Appendix

Sample Goal-Setting Form

Patient's 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 Medical Management Visit Form

Patient's Name: _____ **ID#**_____

Date: _____ **Week#:** _____ **Dose:** _____ mg ☐ No Show

Heroin/cocaine or other illicit drug use since last visit?

_____

Symptoms or signs that might indicate return to use (e.g., changes in mood, physical appearance)?

_____

Since the last visit, are there any problems with the following:

			If yes, explain
Drug Use	☐ Yes	☐ No	_____
Alcohol Use	☐ Yes	☐ No	_____
Psychiatric	☐ Yes	☐ No	_____
Medical	☐ Yes	☐ No	_____
Employment	☐ Yes	☐ No	_____
Social/Family	☐ Yes	☐ No	_____
Legal	☐ Yes	☐ No	_____

Any new problem to add to Treatment Plan Review? ☐ Yes ☐ No

_____

Plan to address any new problem _____

_____

Participation in Narcotics Anonymous or Alcoholics Anonymous since last visit? ☐ Yes ☐ No

Length of Session: _____ Healthcare Professional Signature: _____

D. Fiellin, December 3, 2016 (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.[384]

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 and 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.
- 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 per day 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 are 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, 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 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 is updated periodically; the most current version is available online (https://www.asam.org/docs/default-source/advocacy/sample-diversion-policy.pdf?sfvrsn=6).

Adapted with permission.[385]

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

***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.*

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.[386] Hospital-based providers can take this opportunity to initiate long-term medication maintenance.[387,388]

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.[389] 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.

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.

OPIOID-RELATED
inpatient hospital stays
INCREASED 117%
nationally from 2005 to 2016.[390,391]

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.

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.**[392] 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.[393] 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.[394] 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.[395]

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.[396] 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.[397]

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.**[398]

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.

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.

> **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.**

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.[399] However, as with any patient, use nonopioid multimodal pain management when possible to minimize reliance on opioids and maximize pain control.[400]

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.

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[401,402] and starting patients on buprenorphine in the ED.[403]

Buprenorphine Induction in the Hospital Setting

Patients admitted to the hospital for medical conditions incident to OUD can undergo medically supervised withdrawal or receive buprenorphine maintenance treatment during their inpatient stay.[404] 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.[405] 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.

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.

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/product/Federal-Guidelines-for-Opioid-Treatment-Programs/PEP15-FEDGUIDEOTP).
- 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/product/In-Brief-Rural-Behavioral-Health-Telehealth-Challenges-and-Opportunities/SMA16-4989).
- How certified community behavioral health clinics can use telehealth approaches to expand their services (www.samhsa.gov/section-223/care-coordination/telehealth-telemedicine).

> **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.**

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.

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.[406]

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