Opioid Use Disorder: Pharmacotherapy Part 1

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Part 3 Contents

Part 3: Pharmacotherapy for Opioid Use Disorder

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.

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 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.

Source: Weiss et al. (2017)[1]

Scope of the Problem

The United States is experiencing an opioid addiction epidemic.[2] In 2016, an estimated 2.1 million Americans had OUD.[3] 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.[4] 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.

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

Exhibit 3.1 Key Terms

Addiction: As defined by the American Society of Addiction Medicine, "a primary, chronic disease of brain reward, motivation, memory, and related circuitry."[5] 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,[6] 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 with 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.[7]

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.

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).

Exhibit 3.1 Key Terms

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.

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://pcssmat.org/).

Chapter 3A: Overview of Pharmacotherapy for Opioid Use Disorder

There are three Food and Drug Administration (FDA)-approved medications used to treat opioid use disorder (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.

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

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).

Introduction to Medications That Address OUD

Methadone

Methadone is the most used and most studied OUD medication in the world.[8,9] The World Health Organization (WHO) considers it an essential medication.[10] 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.[11,12,13] (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.

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 (http://store.samhsa.gov/shin/content//PEP15-FEDGUIDEOTP/PEP15-FEDGUIDEOTP.pdf).

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.[14] 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.

Exhibit 3A.1. OUD Medications: An Overview[15,16]

Category	Buprenorphine*	Methadone	Extended-Release Injectable Naltrexone (XR-NTX)**
Appropriate Patients	Typically for patients with OUD who are physiologically dependent on opioids.	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-	**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.

Exhibit 3A.1. OUD Medications: An Overview[15,16]

Category	Buprenorphine*	Methadone	Extended-Release Injectable Naltrexone (XR-NTX)**
	tolerance and opioid receptor occupancy.		
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:** • 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.
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.	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. Any pharmacy can fill a prescription for sublingual or buccal formulations. OTPs can administer/dispense by OTP physician order without a waiver.	SAMHSA-certified OTPs can provide methadone for daily onsite administration or at-home self-administration for stable patients.	Physicians, NPs, or PAs 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.

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.[17,18,19] (See Part 1 and Part 3 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 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.**[20] 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.[21,22]

The oral formulation of naltrexone is not widely used to treat OUD because of low rates of patient acceptance and high rates of nonadherence leading to a lack of efficacy.[23] 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.

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).

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.[24] Buprenorphine treatment is available throughout the world. WHO includes it in its list of essential medicines.[25] (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.[26] 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

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.

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. 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.[27] 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).

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).

Resource Alert: How To Obtain a Waiver To Prescribe Buprenorphine

- Learn how to qualify for a DATA 2000 physician waiver: www.samhsa.gov/medication-assisted-treatment/buprenorphine-waiver-management/qualify-for-physician-waiver
- Learn how to qualify for a NP or PA waiver: www.samhsa.gov/medication-assisted-treatment/qualify-nps-pas-waivers
- Learn how waivered physicians can increase their patient limit from 30 to 100, and then to 275 patients: www.samhsa.gov/sites/default/files/programs_campaigns/medication_assisted/understanding-patient-limit275.pdf

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,[28] 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).[29,30,31,32]
- Patients' preferences. Respect patients' preferences for agonist versus antagonist medication. (See Part 2 of this TIP for an indepth discussion of treatment planning.)

*Methadone or buprenorphine maintenance is recommended for OUD treatment during pregnancy,[33] as these medications have better maternal and infant outcomes than no treatment or medically supervised withdrawal.[34,35,36] Methadone and buprenorphine are not associated with birth defects and have minimal long-term neurodevelopmental impact on infants.[37] However, neonatal abstinence syndrome can occur, which requires hospitalization.[38] The American College of Obstetricians and Gynecologists notes that limited data exist on the safety and effectiveness of naltrexone in pregnancy.[39] 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.[40] 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.[41] Pregnant patients who discontinue naltrexone and return to opioid use should be considered for methadone or buprenorphine treatment.[42]

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.[43] 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.[44] 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. This latter finding is consistent with a recent 12-week study in Norway with 159 participants who were opioid abstinent at the time of random assignment.[45] 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.[46,47,48] Continued treatment with XR-NTX is associated with better outcomes than discontinuing XR-NTX.[49] 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.[50] Pair medically supervised withdrawal with the chance to begin XR-NTX. Discontinuing medication increases risk of return to substance use and overdose death.[51] Stable patients can continue on their selected OUD medication indefinitely as long as it is beneficial.[52,53,54,55]

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.

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.[56,57,58] Even so, shorter term dose reductions alone (formerly, "detoxification") are rarely effective.[59,60,61]

The TIP expert panel does not recommend short-term medically supervised withdrawal alone because of its high rates of return to illicit opioid use.[62,63,64] If patients prefer this approach, it should be provided with psychosocial treatment.[65] 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,[66] 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

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

Principles of OUD Pharmacotherapy

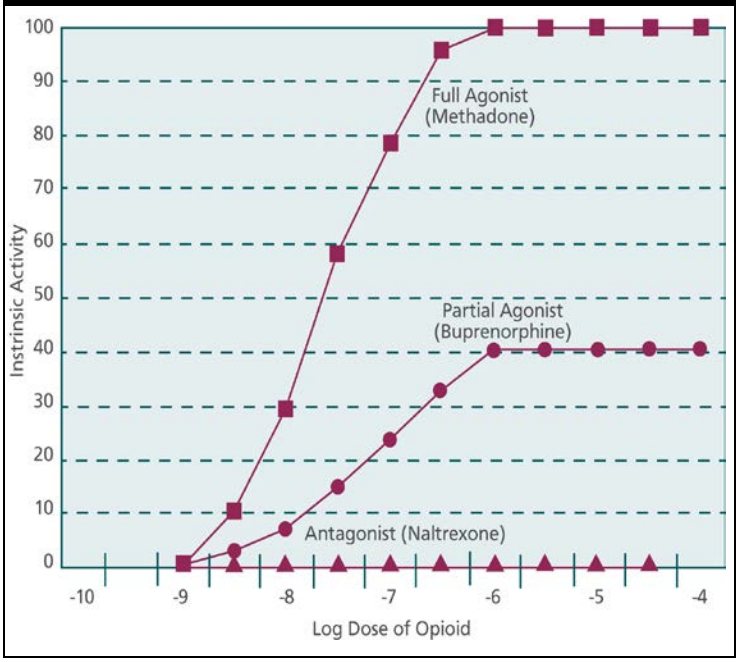
Basic Function

Several factors underlie the development of addiction involving opioids and the difficulty people have in achieving and maintaining abstinence from them. These factors include:[67,68]

- 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).

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.

Exhibit 3A.4. Intrinsic Activity of OUD Medications[69]



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.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[73,74]

Generic/Trade Name	Formulations	Action at the Receptor	FDA Indications	Dosing Regimen
Methadone (Methadone, 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	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 combination product (buprenorphine /naloxone)	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)
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)

Exhibit 3A.5. OUD Medications: Formulations[73,74]				
Generic/Trade Name	**Formulations**	**Action at the Receptor**	**FDA Indications**	**Dosing Regimen**
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 (Revia)	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

Chapter 3B: Methadone

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).[75,76] 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.[77] Other research associates methadone treatment with reduced mortality, criminal behavior, and HIV seroconversion.[78,79,80] 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.[81]

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

In the United States, only opioid treatment programs (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 out of side 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.[82] 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[83] depending on the patient. The average is 24 hours.[84]

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.[85]

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.[86,87]

The liver's CYP450 3A4 enzyme is primarily responsible for metabolizing methadone,[88] although CYP2B6 and CYP2D6 enzymes are also involved.[89] At the start of methadone treatment, methadone can increase CYP3A4 activity and accelerate its own metabolism in some individuals.[90]

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,[91] 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)[92] 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.

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.

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.

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.[93]

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[94] and the unique pharmacology of methadone.

Concurrent substance use disorders 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 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.[95] 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 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.**

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 prescription drug monitoring program [PDMP] database).
  - 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).

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

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.[96]

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.[99,100] 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.[101,102] The prevalence of QTc prolongation among methadone patients is not known with certainty. It has been estimated that about 2 percent of patients in methadone treatment have QTc intervals greater than 500 milliseconds.[103] 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.[104] High methadone doses may be associated with prolonged QTc intervals.[105] Other risk factors include:[106]

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

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.[97] 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.[98]

There is considerable controversy about how best to screen for QTc prolongation without creating barriers to methadone treatment entry.[107] 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.[108] 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,**[109,110] 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 www.crediblemeds.org/pdftemp/pdf/CompositeList.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 to 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.111
  - 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.[112,113,114] 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.[115]

Drug Interactions

Methadone has more clinically significant drug–drug interaction than buprenorphine.[116] 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.

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

Class or Specific Drug	Interaction	Putative Mechanism	Notes
Antiretrovirals			
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			
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's 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's 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's generally safe with careful clinical monitoring.

Exhibit 3B.2. Common Potential Methadone Drug–Drug Interactions			
Class or Specific Drug	**Interaction**	**Putative Mechanism**	**Notes**
Antibiotics			
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			
Ketoconazole, fluconazole	May increase methadone serum levels	Inhibition of CYP enzymes	Little evidence for important clinical effects.
Anticonvulsants			
Carbamazepine, phenytoin, phenobarbital	Reduction in serum methadone levels	Induction of CYP enzymes	Severe opioid withdrawal can occur; will need increased methadone dose.
Antiarrhythmics			
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.
Other Drugs and Specific Classes			
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.[117]			

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).
- Antacid (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 methadone treatment. Monitoring for Zidovudine side effects during treatment is warranted.[119] 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 substance use disorders (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.[120]

- **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 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.
  - **Conduct a pregnancy test:** Pregnant patients with OUD should be treated with methadone or transmucosal buprenorphine.[121,122] 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. If possible, test patients for these infections and refer to treatment as appropriate. The Centers for Disease Control and Prevention recommends hepatitis B vaccination for people seeking treatment for SUDs.[123]

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 (www.ncbi.nlm.nih.gov/books/NBK64244/table/A72912/).

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" 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.

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.

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 only lasts about 1 hour or less, 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.

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

- 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.

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 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.

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 and friends (www.ct.gov/dmhas/lib/dmhas/publications/MAT-InfoFamilyFriends.pdf).

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.[124] 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.[125]
- Have medical disorders that may cause hypoxia, hypercapnia, or cardiac arrhythmias. These include:
  - Asthma, chronic obstructive pulmonary disease, and kyphoscoliosis.
  - Morbid 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[126]). 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.[127] In one such study, 1 mg buprenorphine was the starting dose, which was increased slowly[128] (see Chapter 3D of this TIP). If XR-NTX and buprenorphine are not available, or the patient prefers methadone treatment, consider

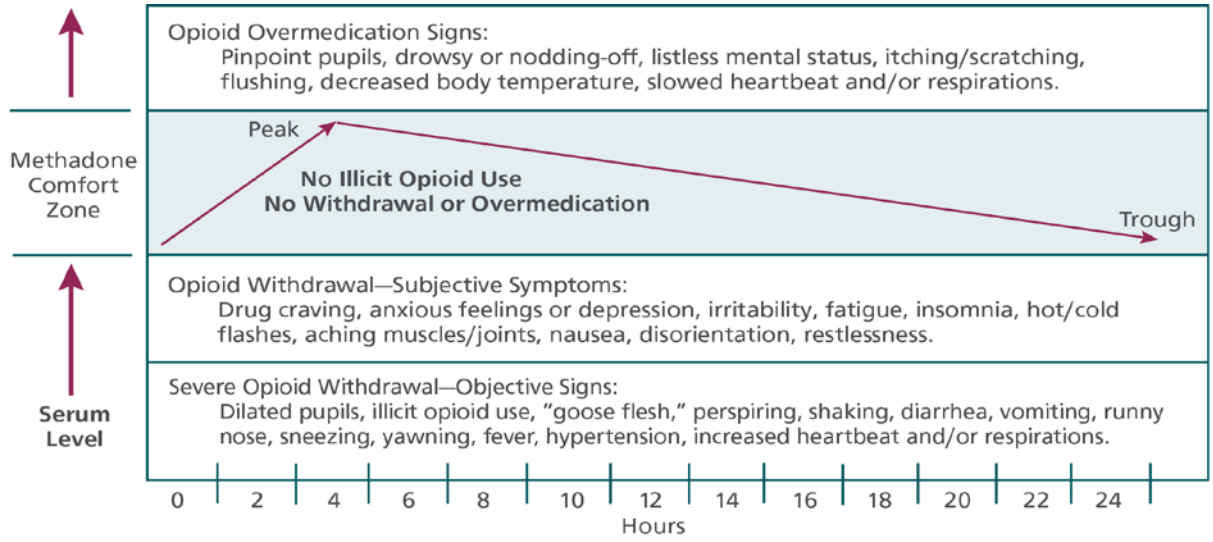
starting methadone at a 5 mg daily dose (as was done in one study[129]) after discussing risks and benefits with the patient.

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).**

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



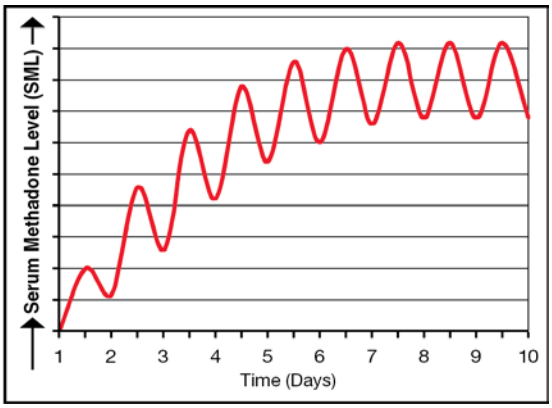
Adapted with permission.[130]

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

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



Adapted with permission.[131,132]

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.[138] 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.[139]

The TIP expert panel advises against arbitrary methadone dosage caps.

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.[140]

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,[141] 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,[142] 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.[143]

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.

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.[144,145] This may require a SAMHSA exception for daily take-home half-doses via a 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[146] is the typical daily range.[147] 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.[148] 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.[149,150] 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.

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* (http://store.samhsa.gov/shin/content/PEP15-FEDGUIDEOTP/PEP15-FEDGUIDEOTP.pdf).

Duration of Methadone Treatment

Longer lengths of stay in methadone treatment are associated with superior treatment outcomes.[151] Leaving methadone treatment is associated with increased risk of death from overdose and other causes.[152,153] Patients should continue as long as they benefit, want to, and develop no contraindications.

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 one with more suitable hours of operation may resolve the problem.

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.

- **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.[154] 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 SAMHSA's *Opioid Overdose Prevention Toolkit* (http://store.samhsa.gov/shin/content//SMA16-4742/SMA16-4742.pdf).

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.[155,156] 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* (http://store.samhsa.gov/shin/content/PEP15-FEDGUIDEOTP/PEP15-FEDGUIDEOTP.pdf).

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 (http://store.samhsa.gov/shin/content/PEP15-FEDGUIDEOTP/PEP15-FEDGUIDEOTP.pdf).

Chapter 3B: Appendix

Sample Standard Consent to Opioid Maintenance Treatment Form for OTPs

CONSENT TO PARTICIPATE IN METHADONE OR BUPRENORPHINE TREATMENT

Patient 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 prescriber, 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's 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.

Sample Standard Consent to Opioid Maintenance Treatment Form for OTPs

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 (known as 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.[157]

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.[158] 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.[159]

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.[160]

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.**[161]

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.[162]

XR-NTX is more effective than placebo[163] or no medication[164] in reducing risk of return to opioid use.[165] 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,[166] 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. No differences were found between XR-NTX and buprenorphine in terms of treatment retention or reduction in illicit opioid use.[167]

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, cause withdrawal when stopped, or 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.[168]

XR-NTX: IM injection causes a transient peak blood concentration 2 hours after injection and another at 2 to 3 days after injection.[169] 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.[170]

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.[171]

XR-NTX, or "depot naltrexone," is encapsulated in biodegradable polymer microspheres. **It provides opioid blockade by delivering steady naltrexone concentrations for about 1 month.**[172] 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:[173]

- 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.[174,175]

- **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.[176] There is active research on approaches to initiate XR-NTX more quickly for patients physically dependent on opioid agonists.[177]
- **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.[178] 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.

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.**[179]

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.

Exhibit 3C.1. Naloxone Challenge

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.

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.[180]

- **Monitor patients with OUD for depression and suicidal ideation.** Naltrexone use has been occasionally associated with dysphoria,[181] 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.[182] 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.

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):[183]

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

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).

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.[184]
  - **Assess liver function.** Obtain liver function tests followed by periodic monitoring at 6- or 12-month intervals during treatment.[185]
  - **Obtain kidney function tests** (e.g., creatinine) for people who inject drugs.
  - **Conduct hepatitis and HIV tests.** Hepatitis B and C are common among patients entering naltrexone treatment. HIV infection is also prevalent. If possible, test the patient for these infections and refer to treatment as appropriate. The Centers for Disease Control and Prevention recommends hepatitis B vaccine for individuals seeking treatment for SUDs.[186]

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 (Exhibit 3C.1).

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

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.[187]

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:[188]

- **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).
- **Have not responded well to prior adequate treatment** with opioid agonist therapy.[189]
- **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.[190]
- **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

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.

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.

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.

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.

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.

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

Patients who test the opioid blockade of XR-NTX may discontinue use because of the blocking of the euphoric effects of illicit opioids.[191] 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).

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.

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 (www.ct.gov/dmhas/lib/dmhas/publications/MAT-InfoFamilyFriends.pdf).

- 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:[192]

- 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 SAMHSA's *Opioid Overdose Prevention Toolkit* (http://store.samhsa.gov/shin/content//SMA16-4742/SMA16-4742.pdf).

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[193] and more recently refined in research settings.[194,195,196]

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 for patients who need medically supervised opioid withdrawal. Rapid induction approaches are likely beyond the scope of general outpatient 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.[197] 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,*[198] 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.[199]

The TIP expert panel doesn't 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.

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,[200] a clinical practice guideline published by the Department of Veterans Affairs and Department of Defense,[201] and a Cochrane review.[202]

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.[203,204]
- **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.[205]

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.[206] Some patients will initially test the opioid blockade with illicit opioids and then discontinue opioid use. However, others will continue using illicit opioids.[207]

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 /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 to 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.

Sample 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 be 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 me and my healthcare provider.
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. I 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 Name (print): _____ Patient Signature _____ Date: _____

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

Adapted with permission.[208]

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.[209]

Key Techniques for Reducing Injection Site Reactions.[210]

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 m

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

Substance Abuse and Mental Health Services Administration.
Medications for Opioid Use Disorder.
Treatment Improvement Protocol (TIP) Series 63.
HHS Publication No. (SMA) 18-5063.
Rockville, MD: Substance Abuse and
Mental Health Services Administration, 2018.