CLINICAL GUIDELINES PROGRAM
NEW YORK STATE DEPARTMENT OF HEALTH AIDS INSTITUTE | HIV · HCV · SUBSTANCE USE · LGBT HEALTH

Treatment of Opioid Use Disorder

Lead Author: Chinazo O. Cunningham, MD, MS, with the Substance Use Guideline Committee, August 2019

Contents

Treatment of Opioid Use Disorder

Purpose and Development of This Guideline

Lead Author: Chinazo O. Cunningham, MD, MS, with the Substance Use Disorder Guideline Committee, August 2019

This guideline on the treatment of opioid use disorder (OUD) was developed by the New York State (NYS) Department of Health (DOH) AIDS Institute (AI) to guide primary care providers and other practitioners in NYS in treating patients with OUD.

This guideline aims to:

- Increase the number of clinicians in outpatient settings offering evidence-based treatment to individuals with opioid use disorder.
- Increase the number of New York State residents with opioid use disorder who are engaged in treatment.
- Reduce the number of opioid-related overdoses and deaths in New York State.
- Promote a harm reduction approach to treatment of all substance use disorders (SUD), which involves practical strategies and ideas aimed at reducing the negative consequences associated with opioid use.
  - See the NYSDOH AI guideline *Harm Reduction Approach to Treatment of All Substance Use Disorders*.

Role of NYS Primary Care Providers in the Treatment of Opioid Use Disorder

Primary care providers in NYS play an essential role in identifying and treating opioid use disorder (OUD) in their patients. Effective treatment exists for OUD and can be delivered in an outpatient setting, thus increasing access to evidence-based treatment for individuals with OUD. OUD is a chronic condition that can be successfully managed long-term in a primary care setting.

In light of the opioid crisis, all clinical care providers in NYS, including those who deliver primary care, should be informed about treatment options for OUD.

Development of This Guideline

This guideline was developed by the NYSDOH AI Clinical Guidelines Program, which is a collaborative effort of the NYSDOH AI Office of the Medical Director and the Johns Hopkins University School of Medicine, Division of Infectious Diseases.

Established in 1986, the goal of the Clinical Guidelines Program is to develop and disseminate evidence-based, state-of-the-art clinical practice guidelines to improve the quality of care throughout NYS for people who have HIV, hepatitis C virus, or sexually transmitted infections; people with substance use issues; and members of the LGBTQ community. NYSDOH AI guidelines are developed by committees of clinical experts through a consensus-driven process.

The NYSDOH AI charged the Substance Use Disorder Guidelines Committee with developing evidence-based clinical recommendations to guide primary care and other medical care providers in treating individuals with OUD. The resulting recommendations are based on extensive review of the medical literature and reflect consensus among the committee members. Each recommendation is rated for strength and quality of evidence based on the rating scheme below. If a recommendation is based on expert opinion, the rationale for the opinion is provided in the text.

AIDS Institute HIV Clinical Guidelines Program Recommendations Rating Scheme	
Strength of Recommendation	**Quality of Supporting Evidence**
A = Strong	1 = At least 1 randomized trial with clinical outcomes and/or validated laboratory endpoints
B = Moderate	2 = One or more well-designed, nonrandomized trial or observational cohort study with long-term clinical outcomes
C = Optional	3 = Expert opinion

Definition of Terms

Lead Author: Chinazo O. Cunningham, MD, MS, with the Substance Use Guideline Committee, August 2019

Box 1: Terms Used in This Guideline	
Substance use	Alcohol or drug use.
Illicit drug use	Use of non-prescription medication or drug.
Substance use disorder (SUD)	*Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)* diagnosis.
SUD treatment	Pharmacologic, psychosocial, or harm reduction intervention for individuals with SUD.
Pharmacologic treatment	Replaces "medication-assisted treatment" (MAT).
Medication	Pharmacologic agent used to treat SUD (e.g., methadone).
Harm reduction • See the NYSDOH AI guideline *Harm Reduction Approach to Treatment of All Substance Use Disorders*.	In the clinical context, harm reduction is an approach and a set of practical strategies targeted to reduce the negative consequences associated with substance use. It is founded on respect for and the rights of those individuals who use drugs [adapted from the Harm Reduction Coalition]. Strategies for reducing harms associated with opioid use are discussed below.

Goals of Treatment for Opioid Use Disorder

Lead Author: Chinazo O. Cunningham, MD, MS, with the Substance Use Guideline Committee, August 2019

The United States is in the midst of an unprecedented opioid crisis, with dramatic increases in opioid use, opioid use disorder (OUD), and opioid-related overdose deaths [Rudd, et al. 2016; SAMHSA 2017; Scholl, et al. 2018]. In the United States in 2017, opioid overdose deaths increased to 47,600 (14.9/100,000) from 42,249 (13.3/100,000) in 2016 and 33,091 (10.4/100,000) in 2015 [Rudd, et al. 2016; Scholl, et al. 2018]. By comparison, there were 8,407 (3.0/100,000) opioid overdose deaths in the United States in 2000 [NCHS 2017].

Similar steep increases in the number of opioid overdose deaths have been observed in New York State (NYS) and New York City. In 2017, there were 2,137 (19.1/100,000) opioid overdose deaths in NYS (excluding New York City) and 1,487 (21.2/100,000) in New York City [Colon-Berezin, et al. 2019; NYSDOH 2019].

Although pharmacologic treatment of OUD improves survival, only approximately 17.5% of Americans with OUDs received any specialty treatment in 2016, the most recent year for which data are available [SAMHSA 2017; Sordo, et al. 2017; Larochelle, et al. 2018]. Given the opioid epidemic's devastating effects on individuals, families, and communities, evidence-based treatment of OUD is urgently needed. Scaled-up and widely implemented, effective treatment for OUD has the potential to curb the opioid epidemic.

A traditional goal of OUD treatment is long-term cessation of opioid use. Because this goal is not achievable for many patients, alternative goals can lead to substantial improvements in the health and lives of those with OUD. Such alternatives may include:

- Staying engaged in care, which can also facilitate prevention, diagnosis, and treatment of other conditions.
- Reducing opioid use.
- Reducing high-risk behaviors, such as injection drug use and sharing of injection equipment, and reducing related complications, such as infection and overdose.
- Improving quality of life and other social indicators, such as employment, stable housing, and risk of incarceration.

As with the treatment goals for other chronic illnesses, OUD treatment goals are individualized and are likely to change over time. It is important for healthcare providers and patients to discuss, agree on, and revisit OUD treatment goals explicitly and regularly. In general, if patients are not able to meet their goals, intensifying treatment with more frequent visits, behavioral interventions, mental health assessment and treatment, and increased doses of medication may be warranted (see *Individualized Follow-Up during Outpatient Substance Use Disorder Treatment*).

○ See the NYSDOH AI guideline *Harm Reduction Approach to Treatment of All Substance Use Disorders*.

Pharmacologic Treatment of Opioid Use Disorder

Lead Author: Chinazo O. Cunningham, MD, MS, with the Substance Use Guideline Committee, August 2019

☑ RECOMMENDATIONS: PHARMACOLOGIC TREATMENT OF OPIOID USE DISORDER

- Clinicians should offer pharmacologic treatment to all patients with opioid use disorder. (A1)
- Clinicians should *not* exclude patients from pharmacologic treatment due to lack of participation in structured psychosocial therapy, such as general counseling, cognitive behavioral therapy, or contingency management. (A1)
  - Note: If a patient is court-ordered to participate in psychosocial therapy, the clinician providing pharmacologic treatment should partner with the patient to ensure compliance with the court order.
- Clinicians should not exclude patients from pharmacologic treatment solely due to co-occurring substance use disorder(s) or other substance use. (A2)
- Because opioid use disorder is a chronic condition, clinicians should recommend long-term pharmacologic treatment, which, in some cases, may be lifelong. (A1)
- Clinicians should offer pharmacologic treatment to patients with opioid use disorder who are not actively using opioids but are at risk of relapse or overdose. (B3)
- Before a patient with opioid use disorder who has been treated for an opioid overdose or a complication related to opioid use leaves an acute care setting, clinicians should initiate or recommend pharmacologic treatment. (A1)
- Clinicians should provide or prescribe naloxone to all patients with opioid use disorder so they are prepared in case of an opioid overdose (A2) and should encourage patients to have their partners, families, and household or other close contacts trained to use naloxone. (A3)

Treatment of a Chronic Condition

Opioid use disorder is a chronic condition: Substance use disorders (SUDs), including opioid use disorder (OUD), have become more widely recognized as chronic conditions [McLellan, et al. 2014]. OUD is associated with significant and persistent changes in brain chemistry and function. Naturally occurring endogenous opioids in the brain act on opioid receptors to produce effects on cognition, emotion, pain, sleep, and other domains [Maldonado 2010]. With repeated exposure to external (exogenous) opioids, the brain's opioid system may be overtaken and may no longer be able to self-regulate [Volkow and Koob 2015; Volkow, et al. 2019]. When this occurs, over time, tolerance to opioids develops, the brain produces lower levels of endogenous opioids, and a larger dose of exogenous opioids is required to obtain the same effects [Williams, et al. 2013; Volkow, et al. 2016]. In addition, a reduction of opioid levels leads to opioid withdrawal syndrome, which has been well-defined [Kampman and Jarvis 2015].

The majority of people who are exposed to exogenous opioids do not develop OUD, and predicting which individuals will develop OUD is difficult. OUD is the result of a multifactorial process involving biologic and environmental influences. With no cure currently available, OUD generally requires long-term management [Gruber, et al. 2008; Woody, et al. 2008; Weiss, et al. 2011; Sigmon, et al. 2013; Fiellin, et al. 2014].

Effective medications: This committee strongly recommends that clinicians offer pharmacologic treatment to all patients diagnosed with OUD (see *American Psychiatric Association > Opioid Use Disorder > Opioid Use Disorder Symptoms*). Currently, 3 medications are approved by the U.S. Food and Drug Administration (FDA) for treatment of OUD—methadone, buprenorphine (BUP), and extended-release injectable naltrexone. All 3 medications act on the mu opioid receptor—methadone as a full opioid agonist, BUP as a partial opioid agonist, and naltrexone as an opioid antagonist. Methadone and BUP are both opioids; naltrexone is not. Decades of clinical research support the efficacy of medications in reducing opioid use and improving retention in treatment among individuals with OUD [Dole and Nyswander 1965; Mello and Mendelson 1980; Ling and Wesson 2003; Minozzi, et al. 2011; Mattick, et al. 2014]. For a discussion of each medication, see the *Treatment Options* section of this guideline.

Psychosocial treatment interventions for OUD, alone or in combination with pharmacologic therapy, may be effective for some patients. However, clinical trial results have consistently demonstrated that pharmacologic treatment is more effective than non-pharmacologic treatment of OUD in reducing illicit opioid use, improving retention in care, and improving other psychosocial and medical conditions [Humphreys, et al. 2004; Amato, et al. 2011b, 2011a; Weiss, et al. 2011; Ruetsch, et al. 2012; Tetrault, et al. 2012; Fiellin, et al. 2013]. However, when psychosocial treatment is mandated by the criminal justice system, child welfare, or other agencies, care providers should partner with patients to comply with all requirements.

Individuals should not be excluded from pharmacologic OUD treatment based on their use of other substances unless there are contraindications to the OUD medications and the risks outweigh the consequences of untreated OUD [Sullivan LE, et al. 2011; Cunningham, et al. 2013; Payne, et al. 2019]. Studies have demonstrated no significant differences in OUD treatment retention or self-reported opioid use between individuals with OUD who used cocaine during the study and those who did not [Sullivan LE, et al. 2011; Cunningham, et al. 2013]. The FDA issued a *Drug Safety Communication* in 2017 urging caution in withholding methadone or BUP from patients using benzodiazepines or alcohol, noting that the harm of not treating OUD outweighs the risk of adverse events associated with combining the medications [FDA 2017]. Co-occurring substance use may influence individual treatment plans but should not be the sole reason for excluding patients from pharmacologic OUD treatment.

Long-term maintenance vs. withdrawal management: Several randomized clinical trials have compared long-term pharmacologic maintenance treatment to withdrawal management (commonly known as "detox"), and the results consistently demonstrate that long-term pharmacologic maintenance treatment is more effective at reducing illicit opioid use and retaining patients in treatment [Gruber, et al. 2008; Woody, et al. 2008; Weiss, et al. 2011; Sigmon, et al. 2013; Fiellin, et al. 2014]. Furthermore, discontinuation of OUD treatment increases the risk of overdose among patients whose tolerance may have decreased during treatment [Kampman and Jarvis 2015]. Despite clear evidence supporting the benefits of long-term pharmacologic treatment, there is limited research to guide the specific duration.

Clinicians should offer pharmacologic therapy for OUD to individuals who may not be actively using opioids but who are at risk of resuming opioid use. Two important risk factors for relapse and overdose among individuals with OUD are a history of overdose and leaving a highly controlled setting, such as prison, jail, hospital, or other treatment facility [Binswanger, et al. 2013; Olfson, et al. 2018].

Treatment providers: In 2000, the U.S. Congress passed the *Drug Addiction Treatment Act (DATA)*, which permits qualified clinicians to treat OUD with schedule III, IV, and V controlled substances outside of specialty drug treatment settings. BUP and naltrexone can be prescribed in any setting. However, to prescribe any formulation of BUP, currently, clinicians must apply for a waiver, which requires training and approval by the Substance Abuse and Mental Health Services Administration (SAMHSA) Center for Substance Abuse Treatment (CSAT). Methadone treatment may be provided only in specialty opioid treatment programs (OTPs), which are also certified by CSAT and single state substance abuse agencies. However, all 3 medications can be administered in any acute care settings even if clinicians do not have waivers to prescribe BUP.

Treatment settings: Pharmacologic treatment for OUD in primary care settings reduces illicit opioid use and improves retention in treatment [Samet, et al. 2001; Magura, et al. 2007; Mintzer, et al. 2007; Cunningham, et al. 2008; Lucas, et al. 2010; Alford, et al. 2011; Altice, et al. 2011; Fiellin, et al. 2011]. One study examining BUP treatment for OUD in "real-world" primary care settings reported a 12-month retention rate of 74% among participants treated in the primary care clinic and 49% among those referred to OUD treatment outside of the primary care clinic [Lucas, et al. 2010]. In addition,

a study among patients with HIV demonstrated that retention in primary care-based BUP treatment is associated with initiation of antiretroviral therapy and improved viral load suppression [Altice, et al. 2011]. Similarly, a study among patients with HCV reported that retention in primary care-based BUP treatment was associated with a higher likelihood of being evaluated and offered treatment for HCV [Norton, et al. 2017].

Several models of integrated OUD treatment have been developed, reflecting the heterogeneity of primary care settings, resources, and structures. Models include office-based opioid treatment, a nurse care manager model, co-location or collaborative care, a hub-and-spoke model, and telehealth care [Korthuis, et al. 2017]. For a detailed discussion see "*Primary Care-Based Models for the Treatment of Opioid Use Disorder: A Scoping Review*," Korthuis PT, McCarty D, Weimer M, et al. *Ann Intern Med* 2017 Feb 21;166(4).

Clinicians in emergency departments (EDs), other acute care settings, and inpatient hospital settings should initiate pharmacologic treatment before patients leave acute care. In addition, clinicians in these setting should also dispense or prescribe NLX for patients with OUD who are at risk of a fatal opioid overdose. Patients at high risk include those who have been treated for an opioid overdose or a complication related to opioid use and those who are not taking OUD treatment medication. The U.S. Centers for Disease Control and Prevention reported a 30% increase in the number of ED visits for opioid overdose in the United States between July and September 2016 and July and September 2017 [Vivolo-Kantor, et al. 2018]. In 2017, there were 7,096 (63.3/100,000) outpatient ED visits for opioid overdose in NYS (excluding New York City) and 2,166 (25.4/100,000) in New York City [NYSDOH 2019].

EDs have tremendous potential to reach individuals with OUD who are not linked to care and are not taking OUD treatment medications. Studies have demonstrated that initiating BUP treatment in the ED is feasible and cost-effective, and when compared to referral to other care settings, retention in care is higher [D'Onofrio, et al. 2015; Busch, et al. 2017; D'Onofrio, et al. 2017]. A study conducted in an inpatient setting compared patients with OUD who were assigned to either a 5-day course of BUP for opioid withdrawal management or to titration to a stable treatment dose of BUP plus linkage to care after hospitalization [Liebschutz, et al. 2014]. The results demonstrated that 6 months after discharge from the hospital, stabilizing patients with OUD on BUP and linking them to care was more effective in reducing opioid use and retaining patients in treatment than opioid withdrawal management.

For information and implementation guides on providing BUP treatment in EDs, see *ED-Initiated Buprenorphine* from the Yale School of Medicine and *Initiating Buprenorphine Treatment in the Emergency Department* from the National Institute on Drug Abuse.

→ KEY POINTS

- The harm of not treating OUD outweighs the risk of adverse events that may be associated with concurrent use of alcohol or benzodiazepines and methadone or BUP.
- Patients who are seen in EDs or other acute care settings for opioid overdose or complications related to opioid use are at risk of a fatal overdose. Pharmacologic treatment for OUD should be initiated or recommended before the patient leaves the acute care setting. In addition, NLX should be dispensed or prescribed.
- Medical settings should offer all pharmacologic OUD treatment options allowed under state and federal regulations.
- Pharmacologic treatment for OUD with BUP/NLX, other formulations of BUP, and extended-release (XR) naltrexone does not require specialized substance use care or clinics. These medications can be prescribed by medical providers in nonspecialized settings and, ideally, integrated into primary care practice.

Overdose Prevention

Prevention of opioid overdose deaths: In addition to providing treatment for OUD, clinicians should provide or facilitate access to NLX for all patients with OUD so they are prepared in case of overdose [McDonald, et al. 2017; Chimbar 2018]. NLX has been used in medical settings since 1971 to reverse opioid overdose, and in 2006 a NYS law took effect allowing people who are not medical professionals to carry NLX and use it if they believe they are witnessing an opioid overdose. As an opioid antagonist, NLX displaces other opioids from opioid receptors but does not cause opioid effects and does not have the potential for misuse. Clinicians should also encourage patients' family members, friends, or other regular contacts to have NLX on hand and be trained to use it for reversing opioid overdose [Walley, et al. 2013; Coffin, et al. 2016]. Distribution of NLX is a key strategy in NYS and elsewhere to combat opioid overdose deaths. For more information on NYS's NLX assistance program and other overdose prevention strategies, see *Box 2*, below.

Box 2: Opioid Overdose Prevention Resources

- New York State's Opioid Overdose Prevention Program
- NYSDOH AI HIV Education and Training Programs
- New York City: Overdose Prevention Resources for Providers
- Harm Reduction Coalition: Understanding Naloxone
- PrescribeToPrevent.org
- **Pharmacy access to NLX in New York:** All Medicaid managed care plans cover at least one formulation of NLX, and the majority of private insurance plans in NYS also cover NLX.
- **Naloxone Co-payment Assistance Program (N-CAP):** N-CAP covers the cost of NLX co-payments up to $40 to limit out-of-pocket expenses for patients with insurance who obtain NLX at pharmacies. This program is administered by the AIDS Drug Assistance Program (ADAP), so pharmacies must also register with ADAP to participate.
  - Patient-specific prescription: Clinicians can prescribe NLX to patients at risk of experiencing or witnessing an overdose.
  - Pharmacy standing order access: All pharmacies can obtain a non–patient-specific order (standing order) and offer NLX to patients at risk of experiencing or witnessing an overdose. More than 2,000 pharmacies across NYS participate.
- **Registered Opioid Overdose Programs:** Many agencies are eligible to become a registered Opioid Overdose Program (OOP) with the NYSDOH, which allows them to order NLX from NYSDOH or New York City Department of Health and Mental Hygiene for free distribution, particularly to individuals who are uninsured or at high risk of overdose and to those who carry NLX in the line of duty. Registered programs include syringe exchange and drug treatment programs and the New York State Department of Corrections and Community Supervision, which offers NLX to inmates when they are released.

Treatment Options

Lead Author: Chinazo O. Cunningham, MD, MS, with the Substance Use Guideline Committee, August 2019

☑ RECOMMENDATIONS: TREATMENT OPTIONS

- Clinicians should inform patients with opioid use disorder about all available pharmacologic options (buprenorphine, methadone, and extended-release injectable naltrexone) and all formulations, which are listed in *Table 1: Medications for Treatment of Opioid Use Disorder in Nonpregnant Adults*. (A3)

Choosing a Treatment Option

- Clinicians should recommend coformulated buprenorphine/naloxone or methadone as preferred treatments for individuals with opioid use disorder. (A3)
- Clinicians and patients should choose the pharmacologic medication for opioid use disorder based on: (A3)
  - Patient opioid tolerance and prior treatment experiences.
  - Available formulations and adverse effects.
  - Evidence of effectiveness of the different treatment options.
  - Ease of access.
  - Presence of other medical conditions.
  - Insurance coverage.
  - Patient preference.
- If individuals who are treated for opioid use disorder with buprenorphine/naloxone or extended- release naltrexone require opioid analgesics for pain management, clinicians should: (B3)
  - Refer patients to methadone treatment.

☑ RECOMMENDATIONS: TREATMENT OPTIONS

  - If methadone treatment is not available, consult or refer patients to an experienced substance use treatment or pain management provider.
- If individuals have continued symptoms of opioid withdrawal or cravings on a maximum dose of buprenorphine 24 mg/naloxone 6 mg per day, taken as one dose or split into two doses (see *Table 1*) clinicians should:
  - Refer patients to methadone treatment. (A3)
  - If methadone treatment is not available, consult or refer patients to an experienced substance use treatment provider. (A3)
- Clinicians should offer extended-release naltrexone to patients who prefer naltrexone for treatment or who are not able to access treatment with or meet their treatment goals with methadone or buprenorphine/naloxone. (A3)

Healthcare providers should inform patients with opioid use disorder (OUD) about all available pharmacologic treatment options and formulations and engage in shared decision-making about the best setting, medication, and formulation based on an individual patient's treatment goals and preferences.

Buprenorphine

Although buprenorphine (BUP) was developed as an analgesic, several decades ago it was explored as an alternative to methadone for treatment of OUD [Jasinski, et al. 1978; Mello and Mendelson 1980; IOM 1995]. With partial activation, the resulting opioid effects are less intense than those produced by a full opioid agonist, such as methadone or heroin.

Extensive clinical trials and systematic reviews have demonstrated that, compared with placebo, BUP significantly reduces opioid misuse and improves retention in treatment [Ling and Wesson 2003; Mattick, et al. 2014], and there is no significant difference between BUP and methadone treatments in reducing illicit opioid use and retaining patients in treatment [Mattick, et al. 2003; Amato, et al. 2005; Mattick, et al. 2014]. BUP treatment also has been associated with improvements in survival [Schuckit 2016; Sordo, et al. 2017; Larochelle, et al. 2018; Ma, et al. 2018].

Available formulations of BUP alone include sublingual [Ling and Wesson 2003; Mattick, et al. 2014], subcutaneous injection [Lofwall, et al. 2018], and subdermal implant [Smith, et al. 2017]. Coformulated BUP/naloxone (NLX) is available in sublingual and buccal formulations, such as films or tablets.

Methadone

Methadone is a full opioid agonist of the mu opioid receptor. Full activation results in commonly known opioid effects, such as pain reduction, a sense of well-being or pleasure, and respiratory depression.

Clinical use of methadone for the treatment of OUD began in the 1960s [Dole and Nyswander 1965; Jaffe 1969], and numerous studies have demonstrated methadone's effectiveness in reducing illicit opioid use and improving retention in care compared with no treatment [Mattick, et al. 2009, 2014; Kampman and Jarvis 2015]. Methadone treatment has been associated with improvements in survival [Soyka, et al. 2011; Sordo, et al. 2017], reduction in HIV and HCV acquisition and transmission [Lucas, et al. 2010], improvement in quality of life [Giacomuzzi, et al. 2003], improvement in maternal-fetal outcomes [Minozzi, et al. 2008], and reduction in criminal activity [Lind, et al. 2004].

Methadone treatment for OUD is available only in specialty OTPs regulated by federal and state agencies. Regulations limit the number of patients that can be treated in each clinic and require observed dosing until patients are granted take-home doses based on an established list of requirements. These restrictions have contributed to reduced access to methadone treatment for many individuals with OUD [McCance-Katz 2018; SAMHSA 2018].

Naltrexone

Naltrexone is an opioid antagonist (inhibitor) that binds to the mu opioid receptor, causes no opioid effects, and fully blocks opioid agonists (heroin, methadone, and other opioids) from attaching to the mu opioid receptor and causing opioid effects [Bisaga, et al. 2018]. Oral naltrexone is not approved by the FDA for OUD treatment, although it is approved for treatment of alcohol use disorder. However, clinicians can use oral naltrexone to confirm that the patient has been abstinent from opioids, to test whether the patient can tolerate naltrexone before administering an extended-release

(XR) injection, or to supplement XR naltrexone if patients experience cravings or withdrawal symptoms during the 28 days between naltrexone injections.

The long-acting injectable naltrexone formulation (XR naltrexone) became available in 2010. Studies have demonstrated that XR naltrexone is more effective than placebo [Comer, et al. 2006; Gastfriend 2011; Tiihonen, et al. 2012] for treatment of OUD, but only 2 randomized trials directly comparing BUP/NLX and XR naltrexone have been published to date [Tanum, et al. 2017; Lee, et al. 2018b]. In one, a study conducted in the United States, individuals randomized to receive BUP/NLX treatment had better outcomes, including lower opioid relapse rates, than those randomized to receive XR naltrexone [Lee, et al. 2018b]. In the second study, conducted in Norway, retention in treatment and the level of opioid use was similar in those taking BUP/NLX and XR naltrexone [Tanum, et al. 2017]. Neither of these studies was conducted in a primary care setting—the U.S. study was conducted in community-based inpatient settings with outpatient follow-up, and the study in Norway was conducted in addiction clinics, where BUP was administered daily. In addition, participants in the Norway study were required to undergo opioid withdrawal management prior to initiating either OUD treatment.

Choosing a Treatment Option

For OUD treatment in pregnant individuals, see the American College of Obstetrics and Gynecology (ACOG) Opinion on Opioid Use and Opioid Use Disorder in Pregnancy.

This Committee recommends the BUP/NLX co-formulation of BUP as the preferred medication for most individuals treated for OUD outside of a specialty opioid treatment setting. The existing evidence does not clearly identify which OUD treatment medication in which setting may be most beneficial for individual patients. Although extensive clinical studies of BUP, BUP/NLX, methadone, and XR naltrexone exist, few clinical trials provide direct comparisons of these medications. For example, some OUD treatment studies evaluate the same medication but in different treatment settings, such as opioid treatment programs (OTPs) or a primary care setting. In addition, many studies occurred in highly restricted settings where participants were observed closely. These factors add to the challenge of interpreting the evidence and extrapolating it to real-world settings. However, because methadone treatment must be provided in specialized OTPs, OUD treatment in primary care settings is limited to BUP or XR naltrexone.

The BUP/NLX co-formulation is recommended over the mono-formulation of BUP because it is less likely to be misused. When BUP/NLX is taken sublingually, only a miniscule amount of NLX, if any, is absorbed. However, when BUP/NLX is injected, NLX is absorbed, and individuals who have opioids in their system will experience opioid withdrawal. Thus, the BUP/NLX co-formulation serves as a deterrent to medication misuse. However, it is important to acknowledge that most diverted or misused BUP is for the purpose of self-treating OUD and not for euphoria [Carroll, et al. 2018].

With sublingual medication, the BUP/NLX co-formulation is preferred over the BUP mono-formulation except in patients with hypersensitivity or allergies to NLX, which are extremely rare in clinical experience. For OUD treatment in pregnant individuals, see the *American College of Obstetrics and Gynecology (ACOG) Opinion on Opioid Use and Opioid Use Disorder in Pregnancy*.

BUP/NLX is currently preferred over XR naltrexone based on the results of clinical trials [Tanum, et al. 2017; Lee, et al. 2018a] (see discussion above), the practical challenges of initiating and maintaining XR naltrexone treatment, and the low number of patients who choose XR naltrexone over other options [Brooklyn 2018]. For example, initiating treatment with XR naltrexone requires patients to be fully withdrawn from opioids, which is difficult for many patients, particularly in outpatient settings. In the U.S. study described above, 28% (79/283) of participants assigned to XR naltrexone did not complete the induction phase [Lee, et al. 2018b]. The induction process is likely part of the reason few patients choose to take XR naltrexone. In June 2018, of 3,639 patients with OUD being treated in Vermont (where all treatment options are generally available), 2,565 were taking methadone, 1,055 were taking BUP, and 2 were taking XR naltrexone [Brooklyn 2018].

Many individual patient factors influence OUD treatment choice. Two key factors are the patient's opioid tolerance and prior treatment experience. Patients with high levels of opioid tolerance may do best with methadone treatment because of its pharmacologic properties as a full opioid agonist (activator). However, for patients with cardiac conduction disorders, treatment other than methadone may be a better choice because of methadone's effect on Q-T prolongation [FDA 2014].

In addition, individuals who are treated for OUD with BUP/NLX or XR naltrexone and who require opioid analgesics for pain management are likely to have substantial challenges. These patients should be referred for methadone treatment, if it is available, or consult a healthcare provider experienced in substance use disorder (SUD) treatment and pain

management. Pharmacologically, BUP has a high affinity for the mu opioid receptor and blocks other opioids from activating the receptor; naltrexone, an opioid antagonist, also blocks opioids from binding to the mu opioid receptors. The opioid analgesics prescribed for pain are likely to be ineffective if the patient takes BUP/NLX or XR naltrexone for OUD treatment. However, it is important to note that BUP has analgesic effects and can often provide pain relief for patients, especially if dosed 2 or 3 times per day. In addition, similar rates of retention in care and similar decreases in opioid use have been demonstrated in individuals with OUD, with or without pain, who were treated with BUP/NLX [Fox, et al. 2012].

Many individuals with OUD achieve their treatment goals in an outpatient, primary care-based medical setting. When available, intensive OUD treatment settings that provide pharmacologic therapy along with frequent visits and individual and group counseling (e.g., an OTP) may benefit some individuals, including those with co-occurring SUDs, unstable social conditions (e.g., homelessness), or those who have untreated mental illness or mental illness that requires intensive treatment.

Some patients treated with BUP/NLX for OUD may present clinical challenges that warrant consultation with experts in obstetrics, adolescent care, pain management, and other medical specialties. Consultation may be necessary when, for instance, managing the care of patients with chronic pain or patients who have ongoing illicit opioid use or cravings despite a maximal dose of BUP/NLX 24 mg/6 mg daily. In these and other complex situations, clinicians can contact expert consultants through the American Society of Addiction Medicine's *Provider's Clinical Support System (PCSS)*, the *University of California San Francisco (UCSF) Substance Use Warmline*, or by sending an email to buprenorphine@health.ny.gov.

In the decision-making process, clinicians should consider BUP monotherapy as an alternative treatment option for patients with hypersensitivity or allergies to NLX, which are extremely rare in clinical experience. Clinicians should also consider XR naltrexone as an alternative treatment option for OUD and recommend it to individuals who are not able to access methadone or BUP/NLX or are not able to meet their treatment goals with methadone or BUP/NLX [Saxon, et al. 2018; Sullivan MA, et al. 2018]. XR naltrexone may also be considered for patients with OUD and alcohol use disorder.

Implementing Opioid Use Disorder Treatment

Lead Author: Chinazo O. Cunningham, MD, MS, with the Substance Use Guideline Committee, August 2019

See the NYSDOH AI guideline *Harm Reduction Approach to Treatment of All Substance Use Disorders*.

☑ RECOMMENDATIONS: IMPLEMENTING OPIOID USE DISORDER TREATMENT

Buprenorphine/Naloxone (Preferred) in the Primary Care Setting

- Because initiation of buprenorphine/naloxone treatment may induce precipitated withdrawal, clinicians should verify—by observation or patient report—that a patient is already experiencing signs and symptoms of opioid withdrawal before starting treatment. (A2)
- Clinicians should titrate a patient's dose of buprenorphine/naloxone to the dose needed to control the patient's opioid cravings, reduce or prevent withdrawal symptoms, and support the individual's treatment goals. (A3)
- Because home-based, unobserved buprenorphine/naloxone induction and office-based, observed induction are equally effective, clinicians should choose an induction approach based on patient and healthcare provider experience, comfort, and preferences. (B2)
- If tapering buprenorphine/naloxone treatment, clinicians should:
  - Inform patients about the risks of recurrence of use, reduced tolerance, and opioid overdose. (A3)
  - Offer patients a slow tapering schedule to minimize withdrawal symptoms. (B3)

Methadone (Preferred)

- Because methadone cannot be prescribed in an office-based setting for treatment of OUD, clinicians should recommend and refer a patient to a methadone maintenance treatment program if the patient: (A3)
  - Prefers methadone treatment.
  - Cannot access buprenorphine/naloxone.

☑ RECOMMENDATIONS: IMPLEMENTING OPIOID USE DISORDER TREATMENT

- Has continued symptoms of opioid withdrawal or cravings while on the maximum dose of BUP/NLX 24 mg/6 mg daily.

Naltrexone (Alternative) in the Primary Care Setting

- When informing patients about extended-release naltrexone as a treatment option, clinicians should emphasize the strong motivation and adherence required for success. (B1)
- Before administering extended-release naltrexone, clinicians should administer a naloxone challenge, and confirm that the patient has no reaction, to ensure that opioids have been cleared from the system. (A2)

Buprenorphine/Naloxone (Preferred) in the Primary Care Setting

When prescribing buprenorphine/naloxone (BUP/NLX), it is important to inform patients about the effects of BUP in the presence of other opioids. BUP is a partial opioid agonist with a stronger affinity for the mu opioid receptor than heroin, methadone, and other opioids. BUP can displace full opioid agonists from mu opioid receptors and replace them with partial activation. Consequently, an individual who takes BUP after taking another full opioid agonist may experience precipitated opioid withdrawal. To prevent precipitated withdrawal, clinicians should ensure that patients experience mild-to-moderate opioid withdrawal symptoms before initiating BUP/NLX treatment [Lee, et al. 2009; Sohler, et al. 2010; Cunningham, et al. 2011].

→ KEY POINTS

- Clinicians qualified to offer BUP in New York State (NYS) can be located by calling the NYS HOPEline at 1-877-8-HOPENY or using the national *SAMSHA Buprenorphine Practitioner Locator*.
- The NYS prescription drug monitoring program (PDMP) tracks a patient's history of dispensed controlled substances and must be consulted before providing each prescription for BUP/NLX (see *New York State I-STOP/PMP - Internet System for Tracking Over-Prescribing - Prescription Monitoring Program).* However, medications dispensed in opioid treatment programs (OTPs) are not included in the PDMP.

Opioid withdrawal symptoms are listed in *Box 3*, below, and clinical tools are available to measure the severity of opioid withdrawal, including the *Clinical Opioid Withdrawal Scale* (COWS) and the *Subjective Opioid Withdrawal Scale* (SOWS) [Handelsman, et al. 1987; Wesson and Ling 2003]. If a patient taking BUP/NLX takes another opioid, BUP will block the other opioid from activating mu opioid receptors and producing the desired effects.

Box 3: Opioid Withdrawal Symptoms

• Increased heart rate • Chills • Insomnia • Bone or joint aches • Gastrointestinal symptoms (cramping, diarrhea, nausea, vomiting) • Anxiety/irritability "goosebumps" on skin	• Increased sweating • Restlessness • Dilated pupils • Runny nose or tearing • Tremor • Yawning

Induction: During the initial 1 to 3 days of BUP/NLX treatment (induction period), the goal is to control the patient's opioid cravings, reduce or prevent withdrawal symptoms, and reduce illicit opioid use. In general, the initial dose ranges from BUP/NLX 2 mg/0.5 mg to 4 mg/1 mg and should be titrated every 30 to 60 minutes in increments of BUP/NLX 2 mg/0.5 mg to 4 mg/1 mg according to the patient's symptoms. In patients who have prior experience with BUP/NLX or who have high levels of opioid tolerance, clinicians may consider initiating treatment with higher doses of BUP/NLX and titrate up to BUP/NLX 16 mg/4 mg on the first day. For patients with no prior BUP/NLX experience and patients who have been taking long-acting opioids, induction may be more complex, and clinicians may want to start with BUP/NLX 2 mg/0.5 mg and titrate up to BUP/NLX 4 mg/1 mg to 8 mg/2 mg on the first day ("start low and go slow") [Whitley, et al. 2010].

Home-based (unobserved) and office-based (observed) induction of BUP/NLX treatment are safe and effective [Lee, et al. 2009; Gunderson, et al. 2010; Sohler, et al. 2010; Cunningham, et al. 2011]. The choice of setting is based on a patient's

and care provider's comfort, preferences, and previous experience. The primary concern during induction is precipitation of opioid withdrawal, which is uncomfortable but not life-threatening and does not require medical attention. Individuals with opioid use disorder (OUD) who are not on treatment may experience withdrawal symptoms regularly between doses of opioids over the course of many years.

→ KEY POINT

- The goal of BUP/NLX dose titration is to reach a dose of medication that will control a patient's opioid cravings, reduce or prevent withdrawal symptoms, and support the patient's treatment goals.

Maintenance: There is no ideal duration for BUP/NLX treatment for OUD (see discussion of short-term and long-term pharmacologic treatment for OUD in the *Treatment Options* section). Committee members have observed that many patients treated in a primary care setting in the South Bronx, New York, have successfully managed OUD with BUP treatment and had no illicit opioid use for as long as 13 years. Among those patients, very few have been able to successfully taper and stop BUP without resuming opioid use. Studies published to date have not identified clear modifiable factors that predict which patients are likely to have optimal outcomes with BUP treatment. Similar to patients with other chronic illnesses, patients with OUD generally have better outcomes (e.g., reduced opioid use, increased retention in care) if they are white, cis-female, older, have less severe disease, have fewer comorbidities (including mental illness and comorbid substance use), and have higher socioeconomic status [Stein, et al. 2005; Mintzer, et al. 2007; Alford, et al. 2011].

If a patient has a clear desire to taper and stop BUP/NLX treatment, healthcare providers should discuss and evaluate the patient's reasons for doing so. Some patients may associate long-term OUD treatment with the stigma of taking an opioid agonist [Bozinoff, et al. 2018]. If stigma is a predominant factor in a patient's desire to stop BUP/NLX treatment, it is important for clinicians to ensure that the patient understands that OUD is a chronic illness that requires long-term management.

If a decision is made to taper BUP/NLX treatment, healthcare providers should provide patient education and counseling to address the risks of recurrence of use and overdose due to decreased opioid tolerance and offer a slow taper over several months. There are limited data to guide the speed and duration of a BUP/NLX taper. However, a reasonable approach is to reduce the daily dose of BUP/NLX by 10% to 20% per month. Providing a slow taper is likely to lead to less severe opioid withdrawal symptoms and may be easier for patients to tolerate than a rapid taper.

Adverse events: Adverse events with use of BUP/NLX are oral hypoesthesia (sensitivity), glossodynia (burning sensation in mouth), oral mucosal erythema, headache, nausea, vomiting, hyperhidrosis (excessive sweating), constipation, signs and symptoms of withdrawal, insomnia, pain, and peripheral edema [FDA 2010]. See prescribing information for full details.

Methadone (Preferred)

Individuals who have a high tolerance for opioids or who have continued cravings while taking maximal doses of BUP/NLX may require methadone, which is a full opioid agonist, to achieve optimal outcomes. Methadone treatment is available only in specialty OTPs, which are intensive treatment settings. Individuals with OUD who have comorbidities may be better candidates for methadone treatment than for other pharmacologic treatment options. In addition, those with comorbidities, such as untreated serious mental illness or other untreated substance use disorders (e.g., alcohol use disorder or benzodiazepine use disorder), may achieve optimal outcomes in a high-intensity treatment setting.

Clinicians should be aware of OUD treatment options in the patient's community and refer patients to an OTP when appropriate. Because federal policies provide special protection for patients receiving substance use disorder treatment (e.g., *Confidentiality of Substance Abuse Disorder Patient Records, Title 42 Electronic Code of Federal Regulations [CFR] 2*), clinicians who are not affiliated with the OTP must provide written patient consent to obtain information about treatment from the OTP. Communication between clinicians inside and outside of OTPs is important for many reasons, including identification of potential drug-drug interactions, management of methadone side effects, and overall management of patient health.

Dosing: Federal and state agencies regulate the treatment available in specialty OTPs, including the initial and maintenance doses of methadone, frequency of visits (daily or almost daily visits are often required for observed medication administration), and frequency of urine testing.

Adverse events: The adverse events associated with use of methadone include constipation, lightheadedness, dizziness, sedation, nausea, vomiting, and sweating. Methadone use has been associated with life-threatening respiratory depression and QT-prolongation [FDA 2014]. See prescribing information for full details.

Buprenorphine Monotherapy (Alternative)

See the *Buprenorphine/Naloxone (Preferred) in the Primary Care Setting* section, above, for use of sublingual BUP monotherapy.

See *Table 1: Medications for Treatment of Opioid Use Disorder in Nonpregnant Adults*, below, for long-acting formulations of BUP. For additional information on use and administration of BUP subcutaneous *(abdominal) injection* (*Sublocade*) and subdermal implants (*Probuphine*), consult the prescribing information.

Naltrexone (Alternative) in the Primary Care Setting

Clinicians should emphasize the need for adherence with extended release (XR) naltrexone for OUD treatment. Clinical trials evaluating XR naltrexone for OUD treatment have demonstrated that adherence is essential to achieving a reduction in illicit opioid use and improving retention in treatment [Tanum, et al. 2017; Jarvis, et al. 2018; Lee, et al. 2018b]. The initial clinical studies with XR naltrexone were performed in highly motivated individuals who were at risk of losing their jobs because of OUD [Saxon, et al. 2018]. A registry study found that factors associated with longer-term adherence were employment at baseline, private health insurance, normal mental status/minimal mental illness, school attendance, and less prior drug use [Saxon, et al. 2018].

Before initiating XR naltrexone, inform patients of the following:

- There is a risk of prolonged opioid withdrawal if opioids are still in a patient's system when XR naltrexone is administered.
- Unlike BUP and methadone, XR naltrexone will not relieve withdrawal symptoms.
- There may be an increased risk of overdose if opioids are used after stopping treatment with XR naltrexone or toward the end of the 28-day dosing interval. Although overdose can occur when opioids are used after stopping any medication for OUD treatment, the risk is particularly high after stopping XR naltrexone, relative to BUP or methadone, because of the substantial reduction in opioid tolerance with XR naltrexone.

Induction: Prescribing information indicates that individuals should be abstinent from opioids for approximately 7 to 14 days prior to initiating XR naltrexone [FDA, 2013]: 7 days for patients using short-acting opioids and 14 days for patients using long-acting opioids (e.g., methadone, extended-release formulations). During this period of abstinence, individuals with OUD will experience moderate-to-severe withdrawal symptoms (see *Box 3: Opioid Withdrawal Symptoms*, above).

To confirm the length of time since last opioid use, clinicians should perform a naloxone challenge by administering a single intranasal dose (2.0 mg/0.1 cc) of naloxone. In individuals with recent opioid use, this may precipitate opioid withdrawal. If a patient is already taking oral naltrexone, a naloxone challenge is not necessary.

If a patient is naltrexone-naive, it is essential to administer a brief regimen of oral naltrexone to confirm that a patient can tolerate the medication before administering a 28-day injection of XR naltrexone. Oral naltrexone is not approved by the FDA for treatment of OUD, but it is used to initiate and stabilize the treatment cycle for XR naltrexone. After informing patients of potential adverse effects of naltrexone, clinicians can instruct patients to:

- Take 25 mg of oral naltrexone (half of a 50 mg naltrexone tablet).
- After 1 hour, if no adverse effects are experienced, take another 25 mg of oral naltrexone (the second half of the 50 mg tablet).
- If adverse effects are experienced, stop taking oral naltrexone.
- If adverse effects are not experienced, take 50 mg of oral naltrexone once daily for 2 to 3 days.

Once it is confirmed that a patient can tolerate naltrexone, an injection of XR naltrexone (380 mg intragluteal) may be administered every 28 days. If injectable XR naltrexone is not immediately available, oral naltrexone may be taken until the injection is available.

Adverse events: Adverse events with use of XR naltrexone include protracted withdrawal, nausea, vomiting, injection site reactions (including induration, pruritus, nodules and swelling), muscle cramps, dizziness or syncope, somnolence or

sedation, anorexia, decreased appetite, or other appetite disorders [FDA 2010b]. See prescribing information for full details.

Individualized follow-up during outpatient substance use disorder treatment: Ongoing, regular follow-up is essential for support, encouragement, and modification of the treatment plan as needed.

- Follow-up within 2 weeks of treatment initiation allows tailoring of the treatment plan (e.g., change in dose of pharmacologic treatment, addition of support services) according to individual needs.
- As individuals stabilize on treatment, monthly or at least quarterly follow-up allows for ongoing evaluation to ensure that the patient's goals are being met.

Table 1: Medications for Treatment of Opioid Use Disorder in Nonpregnant Adults [a]

Medication [b]	**Dose**	**Considerations for Use**
Preferred Medications		
Buprenorphine/naloxone (BUP/NLX) sub-lingual and buccal, film and tablet (multiple brands; see *Medscape > buprenorphine/naloxone* for more information) **Mechanism:** Partial opioid agonist	• **Initial:** Individualized; BUP/NLX 2 mg/0.5 mg to BUP/NLX 8 mg/4 mg. • **Titration:** Adjust dose in increments or decrements of BUP/NLX 2 mg/0.5 mg or BUP/NLX 4 mg/1 mg to reach a level that will control the patient's opioid cravings and withdrawal symptoms and support treatment goals. • **Maximum dose:** BUP/NLX 24 mg/6 mg taken once per day or split into 2 doses per day.	• By observation and/or patient report, confirm that the patient is experiencing signs and symptoms of opioid withdrawal [c]. • Under the *Drug Addiction Treatment Act*, physicians must qualify for a waiver to prescribe BUP. Physicians must complete 8 hours of required training and an application for the waiver, and nurse practitioners, certified nurse midwives, nurse anesthetists, other advanced practice nurses, and physician assistants must complete an additional 16 hours of training (24 hours total of training). – **New York State:** To contact qualified clinicians, call the NYS HOPEline at 1-877-8-HOPENY or use the Substance Abuse and Mental Health Services Administration (SAMHSA) national *Buprenorphine Practitioner Locator*. – **New York City:** To contact qualified clinicians, see *Opioid Addiction Treatment with Buprenorphine or Methadone > How to Find Treatment*. – For information on applying for a waiver, contact SAMHSA or the American Society of Addiction Medicine's *Provider's Clinical Support System (PCSS)*.
Methadone, oral liquid (multiple brands) **Mechanism:** Full opioid agonist	• **Initial:** Individualized dose based on opioid treatment program (OTP) evaluation. • **Titration:** Individualized to reach a dose that will control the patient's opioid cravings and withdrawal symptoms and support treatment goals.	• For a list of certified OTPs in NYS, contact the *Office of Alcoholism and Substance Abuse Services*.

Table 1: Medications for Treatment of Opioid Use Disorder in Nonpregnant Adults [a]		
Medication [b]	**Dose**	**Considerations for Use**
Alternative Medications		
• BUP monotherapy sublingual tablet (multiple brands) • BUP subdermal implants (Probuphine) [d] • BUP subcutaneous (abdominal) injection (Sublocade) [d] **Mechanism**: Partial opioid agonist	• Tablets: – **Initial:** Individualized, 2 mg to 8 mg. – **Titration:** Increase dose by increments of 2 mg to 4 mg daily over 3 to 4 days to reach a dose that will control the patient's opioid cravings and withdrawal symptoms. • Implants: 4 upper-arm subdermal implants lasting 6 months. • Injection: – **Initial:** 300 mg every 4 weeks. – **Maintenance:** 100 mg to 300 mg every 4 weeks.	• Under the *Drug Addiction Treatment Act*, physicians must qualify a waiver to prescribe buprenorphine. Physicians must complete 8 hours of training and an application for the waiver, and nurse practitioners and physician assistants must complete an additional 16 hours of training. – **New York State:** To contact qualified clinicians, call the NYS HOPEline at 1-877-8-HOPENY or use the Substance Abuse and Mental Health Services Administration (SAMHSA) national *Buprenorphine Practitioner Locator*. – **New York City:** To contact qualified clinicians, see *Opioid Addiction Treatment with Buprenorphine or Methadone > How to Find Treatment*. – For information on applying for a waiver, contact SAMHSA or the American Society of Addiction Medicine's *Provider's Clinical Support System (PCSS)*.
Naltrexone long-acting injectable (XR naltrexone) (Vivitrol) **Mechanism:** Opioid antagonist	• 380 mg intragluteal injections every 28 days.	• Inform patients of the risk of precipitated and protracted opioid withdrawal [e] if opioids are used prior to taking naltrexone. • Emphasize the strong motivation and adherence needed for treatment success. • Warn patients of increased risk of opioid overdose after discontinuing naltrexone, due to increased sensitivity. • Confirm the length of time since last opioid use with an NLX challenge: Administer a single intranasal dose (2.0 mg/0.1 cc) of NLX and observe the patient's reaction. In individuals with recent opioid use, this may precipitate opioid withdrawal. • Prescribe a short course of oral naltrexone to confirm the patient can tolerate the medication. • Contraindications: – Acute hepatitis or liver failure. – Concomitant use of opioid analgesics or opioid agonists (e.g., methadone or buprenorphine).

Table 1: Medications for Treatment of Opioid Use Disorder in Nonpregnant Adults [a]		
Medication [b]	**Dose**	**Considerations for Use**
		– Acute opioid withdrawal. – Positive urine test result for opioids. – Failure of the opioid antagonist challenge test.

Notes:

a. For OUD treatment in pregnant individuals, see the *American College of Obstetrics and Gynecology (ACOG) Opinion on Opioid Use and Opioid Use Disorder in Pregnancy*.

b. Consult full prescribing information for each drug before prescribing.

c. Opioid withdrawal symptoms include increased heart rate, chills, insomnia, bone or joint aches, gastrointestinal symptoms (cramping, diarrhea, nausea, vomiting), anxiety/irritability, "goosebumps" on skin, increased sweating, restlessness, dilated pupils, runny nose or tearing, tremor, and yawning.

d. Use for maintenance after treatment initiation with transmucosal buprenorphine and adjustment to optimal dose.

e. When withdrawal is precipitated abruptly by the administration of an opioid antagonist to an opioid-dependent patient, the resulting withdrawal syndrome can be severe enough to require hospitalization. Symptoms of withdrawal usually appear within 5 minutes of ingestion of naltrexone and can last for up to 48 hours. Changes in mental status include confusion, somnolence, and visual hallucinations, and patients can experience significant fluid losses from vomiting and diarrhea requiring intravenous fluid administration.

References

Alford DP, LaBelle CT, Kretsch N, et al. Collaborative care of opioid-addicted patients in primary care using buprenorphine: five-year experience. *Arch Intern Med* 2011;171(5):425-431. [PMID: 21403039] https://www.ncbi.nlm.nih.gov/pubmed/21403039

Altice FL, Bruce RD, Lucas GM, et al. HIV treatment outcomes among HIV-infected, opioid-dependent patients receiving buprenorphine/naloxone treatment within HIV clinical care settings: results from a multisite study. *J Acquir Immune Defic Syndr* 2011;56 Suppl 1:S22-32. [PMID: 21317590] https://www.ncbi.nlm.nih.gov/pubmed/21317590

Amato L, Davoli M, Perucci CA, et al. An overview of systematic reviews of the effectiveness of opiate maintenance therapies: available evidence to inform clinical practice and research. *J Subst Abuse Treat* 2005;28(4):321-329. [PMID: 15925266] https://www.ncbi.nlm.nih.gov/pubmed/15925266

Amato L, Minozzi S, Davoli M, et al. Psychosocial and pharmacological treatments versus pharmacological treatments for opioid detoxification. *Cochrane Database Syst Rev* 2011a;(9):Cd005031. [PMID: 21901695] https://www.ncbi.nlm.nih.gov/pubmed/21901695

Amato L, Minozzi S, Davoli M, et al. Psychosocial combined with agonist maintenance treatments versus agonist maintenance treatments alone for treatment of opioid dependence. *Cochrane Database Syst Rev* 2011b;(10):Cd004147. [PMID: 21975742] https://www.ncbi.nlm.nih.gov/pubmed/21975742

Binswanger IA, Blatchford PJ, Mueller SR, et al. Mortality after prison release: opioid overdose and other causes of death, risk factors, and time trends from 1999 to 2009. *Ann Intern Med* 2013;159(9):592-600. [PMID: 24189594] https://www.ncbi.nlm.nih.gov/pubmed/24189594

Bisaga A, Mannelli P, Sullivan MA, et al. Antagonists in the medical management of opioid use disorders: Historical and existing treatment strategies. *Am J Addict* 2018;27(3):177-187. [PMID: 29596725] https://www.ncbi.nlm.nih.gov/pubmed/29596725

Bozinoff N, Anderson BJ, Bailey GL, et al. Correlates of Stigma Severity Among Persons Seeking Opioid Detoxification. *J Addict Med* 2018;12(1):19-23. [PMID: 28885299] https://www.ncbi.nlm.nih.gov/pubmed/28885299

Brooklyn JR. The Vermont Hub and Spoke Model. National Academies of Sciences, Engineering, Medicine Committee for Medication-Assisted Treatment for Opioid Use Disorder, October 2018; 2018; Washington, DC.

http://www.nationalacademies.org/hmd/~/media/Files/Activity%20Files/MentalHealth/MATopioidUseDisorder/BROOKLYN_hub%20and%20Spoke%20Nat%20Aca%20Sci%20DC%202018.pdf

Busch SH, Fiellin DA, Chawarski MC, et al. Cost-effectiveness of emergency department-initiated treatment for opioid dependence. *Addiction* 2017;112(11):2002-2010. [PMID: 28815789] https://www.ncbi.nlm.nih.gov/pubmed/28815789

Carroll JJ, Rich JD, Green TC. The More Things Change: Buprenorphine/naloxone Diversion Continues While Treatment Remains Inaccessible. *J Addict Med* 2018;12(6):459-465. [PMID: 30095563] https://www.ncbi.nlm.nih.gov/pubmed/30095563

Chimbar LM, Y. Naloxone Effectiveness: A Systematic Review. *J Addict Nurs* 2018;29(3):167-171.

Coffin PO, Behar E, Rowe C, et al. Nonrandomized intervention study of naloxone coprescription for primary care patients receiving long-term opioid therapy for pain. *Ann Intern Med* 2016;165(4):245-252. [PMID: 27366987] https://www.ncbi.nlm.nih.gov/pubmed/27366987

Colon-Berezin C, Nolan ML, Blachman-Forshay J, et al. Overdose deaths involving fentanyl and fentanyl analogs - New York City, 2000-2017. *MMWR Morb Mortal Wkly Rep* 2019;68(2):37-40. [PMID: 30653482] https://www.ncbi.nlm.nih.gov/pubmed/30653482

Comer SD, Sullivan MA, Yu E, et al. Injectable, sustained-release naltrexone for the treatment of opioid dependence: a randomized, placebo-controlled trial. *Arch Gen Psychiatry* 2006;63(2):210-218. [PMID: 16461865] https://www.ncbi.nlm.nih.gov/pubmed/16461865

Cunningham C, Giovanniello A, Kunins H, et al. Buprenorphine treatment outcomes among opioid-dependent cocaine users and non-users. *Am J Addict* 2013;22(4):352-357. [PMID: 23795874] https://www.ncbi.nlm.nih.gov/pubmed/23795874

Cunningham C, Giovanniello A, Li X, et al. A comparison of buprenorphine induction strategies: patient-centered home-based inductions versus standard-of-care office-based inductions. *J Subst Abuse Treat* 2011;40(4):349-356. [PMID: 21310583] https://www.ncbi.nlm.nih.gov/pubmed/21310583

Cunningham C, Giovanniello A, Sacajiu G, et al. Buprenorphine treatment in an urban community health center: what to expect. *Fam Med* 2008;40(7):500-506. [PMID: 18928077] https://www.ncbi.nlm.nih.gov/pubmed/18928077

D'Onofrio G, Chawarski MC, O'Connor PG, et al. Emergency department-initiated buprenorphine for opioid dependence with continuation in primary care: Outcomes during and after intervention. *J Gen Intern Med* 2017;32(6):660-666. [PMID: 28194688] https://www.ncbi.nlm.nih.gov/pubmed/28194688

D'Onofrio G, O'Connor PG, Pantalon MV, et al. Emergency department-initiated buprenorphine/naloxone treatment for opioid dependence: a randomized clinical trial. *JAMA* 2015;313(16):1636-1644. [PMID: 25919527] https://www.ncbi.nlm.nih.gov/pubmed/25919527

Dole V, Nyswander M. A Medical Treatment for Diacetylmorphine (Heroin) Addiction: A Clinical Trial with Methadone Hydrochloride. *JAMA* 1965;193:646-650.

FDA. U.S. Food and Drug Administration. Suboxone (buprenorphine and naloxone) sublingual film for sublingual administration CIII. Prescribing Information. 2010 https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022410s000lbl.pdf [accessed March 20, 2019]

FDA. U.S. Food and Drug Administration. Methadone Hydrochloride Oral Solution Prescribing Information. 2014 https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/090707orig1s003lbl.pdf [accessed March 20, 2019]

FDA. U.S. Food and Drug Administration. FDA urges caution about withholding opioid addiction medications from patients taking benzodiazepines or CNS depressants: careful medication management can reduce risks. 2017 https://www.fda.gov/Drugs/DrugSafety/ucm575307.htm [accessed May 20, 2019]

Fiellin DA, Barry DT, Sullivan LE, et al. A randomized trial of cognitive behavioral therapy in primary care-based buprenorphine. *Am J Med* 2013;126(1):74.e11-77. [PMID: 23260506] https://www.ncbi.nlm.nih.gov/pubmed/23260506

Fiellin DA, Schottenfeld RS, Cutter CJ, et al. Primary care-based buprenorphine taper vs maintenance therapy for prescription opioid dependence: a randomized clinical trial. *JAMA Intern Med* 2014;174(12):1947-1954. [PMID: 25330017] https://www.ncbi.nlm.nih.gov/pubmed/25330017

Fiellin DA, Weiss L, Botsko M, et al. Drug treatment outcomes among HIV-infected opioid-dependent patients receiving buprenorphine/naloxone. *J Acquir Immune Defic Syndr* 2011;56 Suppl 1:S33-38. [PMID: 21317592] https://www.ncbi.nlm.nih.gov/pubmed/21317592

Fox AD, Sohler NL, Starrels JL, et al. Pain is not associated with worse office-based buprenorphine treatment outcomes. *Subst Abus* 2012;33(4):361-365. [PMID: 22989279] https://www.ncbi.nlm.nih.gov/pubmed/22989279

Gastfriend DR. Intramuscular extended-release naltrexone: current evidence. *Ann N Y Acad Sci* 2011;1216:144-166. [PMID: 21272018] https://www.ncbi.nlm.nih.gov/pubmed/21272018

Giacomuzzi SM, Riemer Y, Ertl M, et al. Buprenorphine versus methadone maintenance treatment in an ambulant setting: a health-related quality of life assessment. *Addiction* 2003;98(5):693-702. [PMID: 12751987] https://www.ncbi.nlm.nih.gov/pubmed/12751987

Gruber VA, Delucchi KL, Kielstein A, et al. A randomized trial of 6-month methadone maintenance with standard or minimal counseling versus 21-day methadone detoxification. *Drug Alcohol Depend* 2008;94(1-3):199-206. [PMID: 18243585] https://www.ncbi.nlm.nih.gov/pubmed/18243585

Gunderson EW, Wang XQ, Fiellin DA, et al. Unobserved versus observed office buprenorphine/naloxone induction: a pilot randomized clinical trial. *Addict Behav* 2010;35(5):537-540. [PMID: 20106601] https://www.ncbi.nlm.nih.gov/pubmed/20106601

Handelsman L, Cochrane KJ, Aronson MJ, et al. Two new rating scales for opiate withdrawal. *Am J Drug Alcohol Abuse* 1987;13(3):293-308. [PMID: 3687892] https://www.ncbi.nlm.nih.gov/pubmed/3687892

Humphreys K, Wing S, McCarty D, et al. Self-help organizations for alcohol and drug problems: toward evidence-based practice and policy. *J Subst Abuse Treat* 2004;26(3):151-158; discussion 159-165. [PMID: 15063905] https://www.ncbi.nlm.nih.gov/pubmed/15063905

IOM. Institute of Medicine (US) Committee on Federal Regulation of Methadone Treatment. Federal regulation of methadone treatment. 1995 https://www.ncbi.nlm.nih.gov/books/NBK232105/ [accessed May 20, 2019]

Jaffe J, Zaks, M, Washington, E Experience with the use of methadone in a multimodality program for the treatment of narcotic users. *Inter J Addiction* 1969;4:481-490.

Jarvis BP, Holtyn AF, Berry MS, et al. Predictors of induction onto extended-release naltrexone among unemployed heroin-dependent adults. *J Subst Abuse Treat* 2018;Feb(85):38-44. [PMID: 28449955] https://www.ncbi.nlm.nih.gov/pubmed/28449955

Jasinski J, Pevnick J, Griffith D. Human pharmacology and abuse potential of the analgesic buprenorphine: a potential agent for treating narcotic addiction. *Arch Gen Psychiatry* 1978;35:501-516.

Kampman K, Jarvis M. American Society of Addiction Medicine (ASAM) National Practice Guideline for the Use of Medications in the Treatment of Addiction Involving Opioid Use. *J Addict Med* 2015;9(5):358-367. [PMID: 26406300] https://www.ncbi.nlm.nih.gov/pubmed/26406300

Korthuis PT, McCarty D, Weimer M, et al. Primary care-based models for the treatment of opioid use disorder: A scoping review. *Ann Intern Med* 2017;166(4):268-278. [PMID: 27919103] https://www.ncbi.nlm.nih.gov/pubmed/27919103

Larochelle MR, Bernson D, Land T, et al. Medication for opioid use disorder after nonfatal opioid overdose and association with mortality: a cohort study. *Ann Intern Med* 2018;169(3):137-145. [PMID: 29913516] https://www.ncbi.nlm.nih.gov/pubmed/29913516

Lee JD, Grossman E, DiRocco D, et al. Home buprenorphine/naloxone induction in primary care. *J Gen Intern Med* 2009;24(2):226-232. [PMID: 19089508] https://www.ncbi.nlm.nih.gov/pubmed/19089508

Lee JD, Nunes EV, Jr., Novo P, et al. Comparative effectiveness of extended-release naltrexone versus buprenorphine-naloxone for opioid relapse prevention (X:BOT): a multicentre, open-label, randomised controlled trial. *Lancet* 2018a;391(10118):309-318. [PMID: 29150198] https://www.ncbi.nlm.nih.gov/pubmed/29150198

Lee JD, Nunes EV, Jr., Novo P, et al. Comparative effectiveness of extended-release naltrexone versus buprenorphine-naloxone for opioid relapse prevention (X:BOT): a multicentre, open-label, randomised controlled trial. *The Lancet* 2018b;391(10118):309-318.

Liebschutz JM, Crooks D, Herman D, et al. Buprenorphine treatment for hospitalized, opioid-dependent patients: a randomized clinical trial. *JAMA Intern Med* 2014;174(8):1369-1376. [PMID: 25090173] https://www.ncbi.nlm.nih.gov/pubmed/25090173

Lind B, Weatherburn D, Mattick R, et al. The effectiveness of methadone maintenance treatment in controlling crime: An australian aggregate-level analysis. *Br J Criminol* 2004;45(2):201-211.

Ling W, Wesson DR. Clinical efficacy of buprenorphine: comparisons to methadone and placebo. *Drug Alcohol Depend* 2003;70(2 Suppl):S49-57. [PMID: 12738350] https://www.ncbi.nlm.nih.gov/pubmed/12738350

Lofwall MR, Walsh SL, Nunes EV, et al. Weekly and monthly subcutaneous buprenorphine depot formulations vs daily sublingual buprenorphine with naloxone for treatment of opioid use disorder: A randomized clinical trial. *JAMA Intern Med* 2018;178(6):764-773. [PMID: 29799968] https://www.ncbi.nlm.nih.gov/pubmed/29799968

Lucas GM, Chaudhry A, Hsu J, et al. Clinic-based treatment of opioid-dependent HIV-infected patients versus referral to an opioid treatment program: A randomized trial. *Ann Intern Med* 2010;152(11):704-711. [PMID: 20513828] https://www.ncbi.nlm.nih.gov/pubmed/20513828

Ma J, Bao YP, Wang RJ, et al. Effects of medication-assisted treatment on mortality among opioids users: a systematic review and meta-analysis. *Mol Psychiatry* 2018. [PMID: 29934549] https://www.ncbi.nlm.nih.gov/pubmed/29934549

Magura S, Lee SJ, Salsitz EA, et al. Outcomes of buprenorphine maintenance in office-based practice. *J Addict Dis* 2007;26(2):13-23. [PMID: 17594994] https://www.ncbi.nlm.nih.gov/pubmed/17594994

Maldonado R. [The endogenous opioid system and drug addiction]. *Ann Pharm Fr* 2010;68(1):3-11. [PMID: 20176158] https://www.ncbi.nlm.nih.gov/pubmed/20176158

Mattick RP, Ali R, White JM, et al. Buprenorphine versus methadone maintenance therapy: a randomized double-blind trial with 405 opioid-dependent patients. *Addiction* 2003;98(4):441-452. [PMID: 12653814] https://www.ncbi.nlm.nih.gov/pubmed/12653814

Mattick RP, Breen C, Kimber J, et al. Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. *Cochrane Database Syst Rev* 2009;(3):Cd002209. [PMID: 19588333] https://www.ncbi.nlm.nih.gov/pubmed/19588333

Mattick RP, Breen C, Kimber J, et al. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *Cochrane Database Syst Rev* 2014;(2):Cd002207. [PMID: 24500948] https://www.ncbi.nlm.nih.gov/pubmed/24500948

McCance-Katz EF. SAMHSA: The National Survey on Drug Use and Health: 2018. 2018 https://www.samhsa.gov/data/sites/default/files/cbhsq-reports/Assistant-Secretary-nsduh2018_presentation.pdf [accessed 2019 Aug 21]

McDonald R, Campbell ND, Strang J. Twenty years of take-home naloxone for the prevention of overdose deaths from heroin and other opioids-Conception and maturation. *Drug Alcohol Depend* 2017;178:176-187. [PMID: 28654870] https://www.ncbi.nlm.nih.gov/pubmed/28654870

McLellan AT, Starrels JL, Tai B, et al. Can substance use disorders be managed using the chronic care model? Review and recommendations from a NIDA Consensus Group. *Public Health Rev* 2014;35(2). [PMID: 26568649] https://www.ncbi.nlm.nih.gov/pubmed/26568649

Mello N, Mendelson J. Buprenorphine suppresses heroin use by heroin addicts. *Science* 1980;27:657-659.

Minozzi S, Amato L, Vecchi S, et al. Maintenance agonist treatments for opiate dependent pregnant women. *Cochrane Database Syst Rev* 2008;(2):CD006318. [PMID: 18425946] https://www.ncbi.nlm.nih.gov/pubmed/18425946

Minozzi S, Amato L, Vecchi S, et al. Oral naltrexone maintenance treatment for opioid dependence. *Cochrane Database Syst Rev* 2011;(4):CD001333. [PMID: 21491383] https://www.ncbi.nlm.nih.gov/pubmed/21491383

Mintzer IL, Eisenberg M, Terra M, et al. Treating opioid addiction with buprenorphine-naloxone in community-based primary care settings. *Ann Fam Med* 2007;5(2):146-150. [PMID: 17389539] https://www.ncbi.nlm.nih.gov/pubmed/17389539

Norton BL, Beitin A, Glenn M, et al. Retention in buprenorphine treatment is associated with improved HCV care outcomes. *J Subst Abuse Treat* 2017;75:38-42. [PMID: 28237052] https://www.ncbi.nlm.nih.gov/pubmed/28237052

NYSDOH. New York State - County Opioid Quarterly Report. 2019 https://www.health.ny.gov/statistics/opioid/data/pdf/nys_jan19.pdf [accessed March 16, 2019]

Olfson M, Wall M, Wang S, et al. Risks of fatal opioid overdose during the first year following nonfatal overdose. *Drug Alcohol Depend* 2018;190:112-119. [PMID: 30005310] https://www.ncbi.nlm.nih.gov/pubmed/30005310

Payne BE, Klein JW, Simon CB, et al. Effect of lowering initiation thresholds in a primary care-based buprenorphine treatment program. *Drug Alcohol Depend* 2019;200:71-77. [PMID: 31103879] https://www.ncbi.nlm.nih.gov/pubmed/31103879

Rudd RA, Seth P, David F, et al. Increases in drug and opioid-involved overdose deaths - United States, 2010-2015. *MMWR Morb Mortal Wkly Rep* 2016;65(50-51):1445-1452. [PMID: 28033313] https://www.ncbi.nlm.nih.gov/pubmed/28033313

Ruetsch C, Tkacz J, McPherson TL, et al. The effect of telephonic patient support on treatment for opioid dependence: outcomes at one year follow-up. *Addict Behav* 2012;37(5):686-689. [PMID: 22348921] https://www.ncbi.nlm.nih.gov/pubmed/22348921

Samet JH, Friedmann P, Saitz R. Benefits of linking primary medical care and substance abuse services: patient, provider, and societal perspectives. *Arch Intern Med* 2001;161(1):85-91. [PMID: 11146702] https://www.ncbi.nlm.nih.gov/pubmed/11146702

SAMHSA. Substance Abuse Center for Behavioral Health Statistics and Quality. Results from the 2016 National Survey on Drug Use and Health. 2017 https://www.samhsa.gov/data/sites/default/files/NSDUH-DetTabs-2016/NSDUH-DetTabs-2016.htm [accessed March 20, 2019]

SAMHSA. Reports and Detailed Tables From the 2018 National Survey on Drug Use and Health (NSDUH). 2018 https://www.samhsa.gov/data/nsduh/reports-detailed-tables-2018-NSDUH [accessed 2018 Aug 21]

Saxon AJ, Akerman SC, Liu CC, et al. Extended-release naltrexone (XR-NTX) for opioid use disorder in clinical practice: Vivitrol's Cost and Treatment Outcomes Registry. *Addiction* 2018;113(8):1477-1487. [PMID: 29493836] https://www.ncbi.nlm.nih.gov/pubmed/29493836

Scholl L, Seth P, Kariisa M, et al. Drug and opioid-involved overdose deaths - United States, 2013-2017. *MMWR Morb Mortal Wkly Rep* 2018;67(5152):1419-1427. [PMID: 30605448] https://www.ncbi.nlm.nih.gov/pubmed/30605448

Schuckit MA. Treatment of Opioid-Use Disorders. *N Engl J Med* 2016;375(4):357-368. [PMID: 27464203] https://www.ncbi.nlm.nih.gov/pubmed/27464203

Sigmon SC, Dunn KE, Saulsgiver K, et al. A randomized, double-blind evaluation of buprenorphine taper duration in primary prescription opioid abusers. *JAMA Psychiatry* 2013;70(12):1347-1354. [PMID: 24153411] https://www.ncbi.nlm.nih.gov/pubmed/24153411

Smith L, Mosley J, Johnson J, et al. Probuphine (buprenorphine) subdermal implants for the treatment of opioid-dependent patients. *P & T* 2017;42(8):505-508. [PMID: 28781503] https://www.ncbi.nlm.nih.gov/pubmed/28781503

Sohler NL, Li X, Kunins HV, et al. Home- versus office-based buprenorphine inductions for opioid-dependent patients. *J Subst Abuse Treat* 2010;38(2):153-159. [PMID: 19801178] https://www.ncbi.nlm.nih.gov/pubmed/19801178

Sordo L, Barrio G, Bravo MJ, et al. Mortality risk during and after opioid substitution treatment: systematic review and meta-analysis of cohort studies. *BMJ* 2017;357:j1550. [PMID: 28446428] https://www.ncbi.nlm.nih.gov/pubmed/28446428

Soyka M, Trader A, Klotsche J, et al. Six-year mortality rates of patients in methadone and buprenorphine maintenance therapy: results from a nationally representative cohort study. *J Clin Psychopharmacol* 2011;31(5):678-680. [PMID: 21881461] https://www.ncbi.nlm.nih.gov/pubmed/21881461

Stein MD, Cioe P, Friedmann PD. Buprenorphine retention in primary care. *J Gen Intern Med* 2005;20(11):1038-1041. [PMID: 16307630] https://www.ncbi.nlm.nih.gov/pubmed/16307630

Sullivan LE, Botsko M, Cunningham CO, et al. The impact of cocaine use on outcomes in HIV-infected patients receiving buprenorphine/naloxone. *J Acquir Immune Defic Syndr* 2011;56 Suppl 1:S54-61. [PMID: 21317595] https://www.ncbi.nlm.nih.gov/pubmed/21317595

Sullivan MA, Bisaga A, Pavlicova M, et al. A randomized trial comparing extended-release injectable suspension and oral naltrexone, both combined with behavioral therapy, for the treatment of opioid use disorder. *Am J Psychiatry* 2018:appiajp201817070732. [PMID: 30336703] https://www.ncbi.nlm.nih.gov/pubmed/30336703

Tanum L, Solli KK, Latif ZE, et al. The effectiveness of injectable extended-release naltrexone vs daily buprenorphine-naloxone for opioid dependence: A randomized clinical noninferiority trial. *JAMA Psychiatry* 2017. [PMID: 29049469] https://www.ncbi.nlm.nih.gov/pubmed/29049469

Tetrault JM, Moore BA, Barry DT, et al. Brief versus extended counseling along with buprenorphine/naloxone for HIV-infected opioid dependent patients. *J Subst Abuse Treat* 2012;43(4):433-439. [PMID: 22938914] https://www.ncbi.nlm.nih.gov/pubmed/22938914

Tiihonen J, Krupitsky E, Verbitskaya E, et al. Naltrexone implant for the treatment of polydrug dependence: a randomized controlled trial. *Am J Psychiatry* 2012;169(5):531-536. [PMID: 22764364] https://www.ncbi.nlm.nih.gov/pubmed/22764364

Vivolo-Kantor AM, Seth P, Gladden RM, et al. Vital signs: Trends in emergency department visits for suspected opioid overdoses - United States, July 2016-September 2017. *MMWR Morb Mortal Wkly Rep* 2018;67(9):279-285. [PMID: 29518069] https://www.ncbi.nlm.nih.gov/pubmed/29518069

Volkow ND, Jones EB, Einstein EB, et al. Prevention and treatment of opioid misuse and addiction: A review. *JAMA Psychiatry* 2019;76(2):208-216. [PMID: 30516809] https://www.ncbi.nlm.nih.gov/pubmed/30516809

Volkow ND, Koob G. Brain disease model of addiction: why is it so controversial? *Lancet Psychiatry* 2015;2(8):677-679. [PMID: 26249284] https://www.ncbi.nlm.nih.gov/pubmed/26249284

Volkow ND, Koob GF, McLellan AT. Neurobiologic Advances from the Brain Disease Model of Addiction. *N Engl J Med* 2016;374(4):363-371. [PMID: 26816013] https://www.ncbi.nlm.nih.gov/pubmed/26816013

Walley AY, Xuan Z, Hackman HH, et al. Opioid overdose rates and implementation of overdose education and nasal naloxone distribution in Massachusetts: interrupted time series analysis. *BMJ* 2013;346:f174. [PMID: 23372174] https://www.ncbi.nlm.nih.gov/pubmed/23372174

Weiss RD, Potter JS, Fiellin DA, et al. Adjunctive counseling during brief and extended buprenorphine-naloxone treatment for prescription opioid dependence: a 2-phase randomized controlled trial. *Arch Gen Psychiatry* 2011;68(12):1238-1246. [PMID: 22065255] https://www.ncbi.nlm.nih.gov/pubmed/22065255

Wesson DR, Ling W. The Clinical Opiate Withdrawal Scale (COWS). *J Psychoactive Drugs* 2003;35(2):253-259. [PMID: 12924748] https://www.ncbi.nlm.nih.gov/pubmed/12924748

Whitley SD, Sohler NL, Kunins HV, et al. Factors associated with complicated buprenorphine inductions. *J Subst Abuse Treat* 2010;39(1):51-57. [PMID: 20682186] https://www.ncbi.nlm.nih.gov/pubmed/20682186

Williams JT, Ingram SL, Henderson G, et al. Regulation of mu-opioid receptors: desensitization, phosphorylation, internalization, and tolerance. *Pharmacol Rev* 2013;65(1):223-254. [PMID: 23321159] https://www.ncbi.nlm.nih.gov/pubmed/23321159

Woody GE, Poole SA, Subramaniam G, et al. Extended vs short-term buprenorphine-naloxone for treatment of opioid-addicted youth: a randomized trial. *JAMA* 2008;300(17):2003-2011. [PMID: 18984887] https://www.ncbi.nlm.nih.gov/pubmed/18984887

All Recommendations

Lead Author: Chinazo O. Cunningham, MD, MS, with the Substance Use Guideline Committee, August 2019

☑ ALL RECOMMENDATIONS: TREATMENT OF OPIOID USE DISORDER

Pharmacologic Treatment of Opioid Use Disorder

- Clinicians should offer pharmacologic treatment to all patients with opioid use disorder. (A1)
- Clinicians should *not* exclude patients from pharmacologic treatment due to lack of participation in structured psychosocial therapy, such as general counseling, cognitive behavioral therapy, or contingency management. (A1)
  - Note: If a patient is court-ordered to participate in psychosocial therapy, the clinician providing pharmacologic treatment should partner with the patient to ensure compliance with the court order.
- Clinicians should not exclude patients from pharmacologic treatment solely due to co-occurring substance use disorder(s) or other substance use. (A2)
- Because opioid use disorder is a chronic condition, clinicians should recommend long-term pharmacologic treatment, which, in some cases, may be lifelong. (A1)
- Clinicians should offer pharmacologic treatment to patients with opioid use disorder who are not actively using opioids but are at risk of relapse or overdose. (B3)
- Before a patient with opioid use disorder who has been treated for an opioid overdose or a complication related to opioid use leaves an acute care setting, clinicians should initiate or recommend pharmacologic treatment. (A1)
- Clinicians should provide or prescribe naloxone to all patients with opioid use disorder so they are prepared in case of an opioid overdose (A2) and should encourage patients to have their partners, families, and household or other close contacts trained to use naloxone. (A3)

Treatment Options

- Clinicians should inform patients with opioid use disorder about all available pharmacologic options (buprenorphine, methadone, and extended-release injectable naltrexone) and all formulations, which are listed in *Table 1: Medications for Treatment of Opioid Use Disorder in Nonpregnant Adults*. (A3)

Choosing a Treatment Option

- Clinicians should recommend coformulated buprenorphine/naloxone or methadone as preferred treatments for individuals with opioid use disorder. (A3)
- Clinicians and patients should choose the pharmacologic medication for opioid use disorder based on: (A3)
  - Patient opioid tolerance and prior treatment experiences.
  - Available formulations and adverse effects.
  - Evidence of effectiveness of the different treatment options.
  - Ease of access.
  - Presence of other medical conditions.
  - Insurance coverage.
  - Patient preference.
- If individuals who are treated for opioid use disorder with buprenorphine/naloxone or extended-release naltrexone require opioid analgesics for pain management, clinicians should: (B3)
  - Refer patients to methadone treatment.
  - If methadone treatment is not available, consult or refer patients to an experienced substance use treatment or pain management provider.
- If individuals have continued symptoms of opioid withdrawal or cravings on a maximum dose of buprenorphine 24 mg/naloxone 6 mg per day, taken as one dose or split into two doses (see *Table 1*) clinicians should:
  - Refer patients to methadone treatment. (A3)

☑ ALL RECOMMENDATIONS: TREATMENT OF OPIOID USE DISORDER

  - If methadone treatment is not available, consult or refer patients to an experienced substance use treatment provider. (A3)
- Clinicians should offer extended-release naltrexone to patients who prefer naltrexone for treatment or who are not able to access treatment with or reach their treatment goals with methadone or buprenorphine/naloxone. (A3)

Buprenorphine/Naloxone (Preferred) in the Primary Care Setting

- Because initiation of buprenorphine/naloxone treatment may induce precipitated withdrawal, clinicians should verify—by observation or patient report—that a patient is already experiencing signs and symptoms of opioid withdrawal before starting treatment. (A2)
- Clinicians should titrate a patient's dose of buprenorphine/naloxone to the dose needed to control the patient's opioid cravings, reduce or prevent withdrawal symptoms, and support the individual's treatment goals. (A3)
- Because home-based, unobserved buprenorphine/naloxone induction and office-based, observed induction are equally effective, clinicians should choose an induction approach based on patient and healthcare provider experience, comfort, and preferences. (B2)
- If tapering buprenorphine/naloxone treatment, clinicians should:
  - Inform patients about the risks of recurrence of use, reduced tolerance, and opioid overdose. (A3)
  - Offer patients a slow tapering schedule to minimize withdrawal symptoms. (B3)

Methadone (Preferred)

- Because methadone cannot be prescribed in an office-based setting for treatment of opioid use disorder, clinicians should recommend and refer a patient to a methadone maintenance treatment program if the patient: (A3)
  - Prefers methadone treatment.
  - Cannot access buprenorphine/naloxone.
  - Has continued symptoms of opioid withdrawal or cravings while on the maximum dose of buprenorphine/naloxone 24 mg/6 mg daily.

Naltrexone (Alternative) in the Primary Care Setting

- When informing patients about extended-release naltrexone as a treatment option, clinicians should emphasize the strong motivation and adherence required for success. (B1)
- Before administering extended-release naltrexone, clinicians should administer a naloxone challenge, and confirm that the patient has no reaction, to ensure that opioids have been cleared from the system. (A2)