Opioid use disorder: Pharmacologic management

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INTRODUCTION

Opioids, used medically for pain relief, have analgesic and central nervous system depressant effects, as well as the potential to cause euphoria. Opioid use disorder (OUD) can be related to misuse of pharmaceutical opioids, heroin, or other opioids such as fentanyl and its analogs. OUD is typically a chronic, relapsing illness, associated with significantly increased rates of morbidity and mortality.

Medication for OUD (MOUD) consists of treatment with an opioid agonist or antagonist and is first-line treatment for most patients with an OUD. MOUD appears to reinforce abstinence and improve treatment retention [1-4]. Our approach to treating OUD, including choice of treatment, is discussed elsewhere. Pharmacotherapy for OUD is reviewed here. The epidemiology, clinical manifestations, course, screening, assessment, diagnosis, and psychosocial treatment for OUD are reviewed separately. Other topics including those addressing medically supervised opioid withdrawal, prescription drug misuse, substance use disorder in clinicians, management of OUD during pregnancy, and treatment of acute pain in the patient chronically using opioids are also discussed elsewhere:

- (See "Opioid use disorder: Treatment overview".)
- (See "Opioid use disorder: Epidemiology, clinical features, health consequences, screening, and assessment".)
- (See "Opioid use disorder: Psychosocial management".)

- (See "Opioid withdrawal: Medically supervised withdrawal during treatment for opioid use disorder".)
- (See "Management of acute pain in the patient chronically using opioids for non-cancer pain".)
- (See "Prescription drug misuse: Epidemiology, prevention, identification, and management".)
- (See "Substance use disorders in physicians: Epidemiology, clinical manifestations, identification, and engagement".)
- (See "Substance use disorders in physicians: Assessment and treatment".)
- (See "Opioid use disorder: Overview of treatment during pregnancy".)

APPROACH TO TREATMENT

Our preference is to treat all individuals with opioid use disorder (OUD) with medication for OUD (MOUD) and psychotherapy. We consider OUD to be a chronic condition and treat indefinitely. However, in individuals who are fully free of problematic substance use, are engaged in productive activities, and have stable psychosocial support for at least 6 to 12 months, we support a slow taper off of MOUD at the patient's request. The general approach to selecting treatment for OUD, including selecting among MOUD options, is described separately (algorithm 1). (See "Opioid use disorder: Treatment overview", section on 'Assessment of response' and "Opioid use disorder: Treatment overview", section on 'Duration of therapy for responders'.)

BUPRENORPHINE: OPIOID AGONIST

In individuals with an opioid use disorder (OUD), buprenorphine suppresses withdrawal symptoms, craving, and blocks the effect of other opioids thereby reducing use [1,5,6]. As a partial agonist with high affinity for mu-opioid receptor it displaces other agonists from the receptor (high affinity) potentially precipitating withdrawal (partial agonist) in individuals on opioids. Although individuals treated with buprenorphine are physically dependent upon the medications, they do not typically have the pattern and severity of problematic behaviors associated with use and misuse of heroin or pharmaceutical opioids including fentanyl [7-9].

Choosing among buprenorphine formulations — For most individuals, our initial choice of opioid agonist for the treatment of OUD is with transmucosal buprenorphine. However, we prefer to use longer-acting formulations of buprenorphine in individuals with limited adherence, misuse, and/or diversion of transmucosal buprenorphine. We consider patient

preference and use shared decision-making in formulating the treatment plan. (See "Opioid use disorder: Treatment overview", section on 'Shared decision-making'.)

Buprenorphine is available in daily transmucosal formulations, as an extended-release subcutaneous injection (Sublocade; given every 30 days) that requires an initial period of transmucosal buprenorphine, and as a weekly or monthly subcutaneous injectable formulation (Brixadi) that can be used without a period of transmucosal stabilization.

Transmucosal formulations — Buprenorphine is most commonly administered transmucosally (film strip or tablet) in a combination preparation with naloxone, an opioid antagonist. The combination is used to prevent individuals from crushing the tablets and dissolving them for intravenous injection or dissolving the soluble film for injection [10]. Naloxone has little to no bioavailability or activity when administered sublingually but discourages intravenous buprenorphine misuse since the naloxone can precipitate withdrawal when given parenterally to individuals with physiologic dependence on opioids. The ratio of buprenorphine to naloxone is 4:1, and a variety of dose sizes are available (eg, 2/0.5, 4/1, 8/2, 12/3). Additionally, a sublingual tablet form of buprenorphine/naloxone provides equivalent amounts of the medication as the traditional tablet doses used, but contains a lower dose of buprenorphine. (For example, one of the formulations provides 5.7 mg dose that is equal to 8 mg of buprenorphine.)

A transmucosal formulation of buprenorphine that does not contain naloxone is also available. Although allergy to naloxone is extremely rare, some individuals report an allergy. Additionally, some individuals report unpleasant side effects from the combination formulation that they do not get from the buprenorphine only formulation. This may be due to trace amounts of naloxone that may be absorbed transmucosally [11,12]. In those rare cases, a shared decision-making discussion is needed to decide on the formulation to use. We determine whether to use the non-naloxone formulation on a case-by-case basis.

Standard induction — We use a standard induction in most clinical scenarios. However, in some cases, for example, if the individual presents and is not in early withdrawal or for high levels of physiologic dependence, we often use another protocol, such as low-dose initiation. (See 'Alternative induction methods for specific circumstances' below.)

Timing and site of initiation — When initiating buprenorphine, the individual needs to be abstinent from other opioids long enough to enter a state of mild withdrawal (see 'Assessing for withdrawal' below). Time to reach this state varies as a function of the half-life of the opioid being used by the patient. As examples, withdrawal from heroin or other short-acting opioids

can appear 6 to 12 hours after the last dose, while withdrawal from methadone can appear in 24 to 36 hours.

Induction can be done in the office, emergency department, or at home. When done in the office or emergency department, the buprenorphine is given directly to the patient after assessment for withdrawal. The patient is then given supply of several days lasting until scheduled follow-up appointment. When done at home, the patient receives two to seven days of medication depending upon the patient's circumstances and scheduling of follow-up appointments and is instructed on how to assess for withdrawal. (See 'Assessing for withdrawal' below and "Acute opioid intoxication in adults", section on 'Prevention of recurrent opioid overdose'.)

Assessing for withdrawal — To determine that the patient has entered a state of mild to moderate opioid withdrawal, we observe the patient for early signs of opioid withdrawal such as sweating, tremor, piloerection, irritability, or yawning at the time of initiation. We use a standard measure, the Clinical Opiate Withdrawal Scale (COWS) (table 1). We consider a score of 12 or more on the COWS to be objective evidence of mild to moderate withdrawal. When signs of early withdrawal appear, we begin the induction with buprenorphine. Buprenorphine ameliorates the withdrawal by binding to and activating the mu-opioid receptors [10].

If home induction is planned, we instruct the patient how to determine the presence of sufficient withdrawal to begin induction. We review the objective signs of withdrawal (tremor, piloerection, sweating) and how to differentiate them from subjective symptoms (eg, irritability, restlessness). We often ask the patient to use the Subjective Opiate Withdrawal Scale as a guide to whether they are in mild to moderate withdrawal and whether to begin induction. Scores of 17 or greater indicate that there is a mild to moderate level of withdrawal and that induction can start. Tools and handouts for patients and family members that can be helpful in home inductions can be found in the Providers Clinical Support System. (See "Opioid withdrawal: Medically supervised withdrawal during treatment for opioid use disorder", section on 'Monitoring'.)

Initiating induction — Induction begins with the individual manifesting signs of withdrawal. (See 'Standard induction' above.)

- **Day 1** – We typically start transmucosal buprenorphine at a dose of 4 mg (ie, 4 mg/1 mg of buprenorphine-naloxone). Relief of symptoms may occur in minutes although one to two hours of observation is needed for full effect. We observe the patient for a full two hours. At that time, we reassess for symptoms of withdrawal.

- If withdrawal symptoms persist (eg, COWS ≥6 (table 1)), an additional dose of up to 4 mg can be administered.

- If the individual has sufficient relief of symptoms (COWS <6) we allow the individual to go home. We provide a second dose of buprenorphine for the individual to bring home and take if withdrawal symptoms or craving become prominent before the next morning.

Federal guidelines recommend a maximum dose of 8 mg (ie, 8/2 mg) on the first day. In some cases, for example if the individual has been using fentanyl, higher doses may be needed [13]. Thus, a dose higher than 8 mg can be considered on the first day, although this is generally the exception rather than the rule. Further dose increases can occur on subsequent days, as noted below.

- **Day 2** – The patient is given a single dose consisting of the total of the doses received the first day. We monitor the individual over the next one to two hours.

  - If residual symptoms are present (ie, COWS ≥6 (table 1)), we give another 4 mg (ie, 4 mg/2 mg). We continue to monitor and give 4 mg every two hours depending on COWS score (ie, COWS score ≥6). We give a maximum total dose of 16 mg (ie, 16/4 mg buprenorphine-naloxone) on day 2.

  - If the individual has sufficient relief of symptoms (COWS <6) we allow the individual to go home and provide further maintenance doses. We typically give patients a week supply, but the precise number of days of medication given varies depending upon the patient and their circumstances (eg, social supports at home).

  United States federal and European guidelines recommend a maximum dose on day 2 of 16 mg total (ie, 16/4 mg of buprenorphine-naloxone) [13,14].

- **Maintenance** – We usually do not increase the dose above 16 mg for several days to one week to allow pharmacologic steady state to be reached. Most individuals will stabilize on 8 to 16 mg/day of buprenorphine [15]; however, in some cases, particularly when fentanyl is the primary opioid being used, the individual may need doses up to 32 mg/day [16-18]. The goal of dose maintenance treatment is to ensure there is no opioid withdrawal, no opioid craving, and no or markedly reduced illicit opioid use.

Alternative induction methods for specific circumstances — In specific circumstances, we use a modified induction protocol, such as low-dose initiation or aggressive buprenorphine induction However, evidence to support their use is limited.

- **Low-dose initiation** – Low-dose initiation (also called microdosing) is a method of buprenorphine induction that involves frequent administration of small doses (eg, 0.5 to 1 mg) of buprenorphine, which is initiated while the individual is on full agonist [19,20]. Advocates note that with this method, the transition to buprenorphine/naloxone can begin without waiting for signs of withdrawal. Additionally, frequent low dosing avoids precipitation of withdrawal that would otherwise occur with standard doses of buprenorphine in individuals on opioid agonists. However, most of the evidence for the value of this approach is based upon case reports. The use of low-dose initiation can occur in the following clinical scenarios:

  - **High levels of physical dependence (eg, fentanyl)** – As fentanyl has become more widely misused, there have been reports of difficulties in achieving successful buprenorphine induction in these patients [21]. This may be related to protracted fentanyl clearance in some patients [22], or due to higher levels of physical dependence. We have used low-dose initiation in these individuals to achieve induction. Other options include waiting longer after the last fentanyl use, giving buprenorphine at longer intervals (>2 hours between doses) or using methadone rather than buprenorphine.

  - **Switching from methadone** – We transition individuals from methadone to buprenorphine using low-dose initiation. With this method, the individual can avoid tapering methadone down prior to beginning buprenorphine [23]. In one study, individuals maintained on methadone 100 mg daily received repeated small doses of buprenorphine-naloxone and did not experience significant precipitated withdrawal symptoms [24].

  - **Individuals who present who are not in withdrawal** – In some cases individuals present for induction but have not yet have reached a state of withdrawal. In these cases, we attempt induction with a lower dose of buprenorphine (eg, 1 mg or less) given repeatedly at two-hour intervals while monitoring for withdrawal symptoms.

- **Aggressive** buprenorphine **induction in emergency department settings** – Aggressive buprenorphine induction may mitigate withdrawal more aggressively and facilitate acceptance of buprenorphine and transition to outpatient treatment. Sublingual buprenorphine (monoproduct formulation) induction using an aggressive dosing approach (4 to 8 mg initially; up to ≤32mg) has been safely used in emergency department settings [25,26].

In a retrospective case series of emergency department patients, 391 individuals (579 encounters) with OUD were selected for an aggressive buprenorphine induction (based on history, physical examination, and use of the COWS) [25]. Patients were treated with buprenorphine of up to 32 mg at a rate dependent on severity of withdrawal symptoms and adverse effects. No cases of respiratory depression or sedation or other serious adverse events were reported. These findings may not be generalizable to sublingual formulations other than monoproduct sublingual buprenorphine, and the procedure occurred in a supervised setting (the emergency department).

- **Hospitalized patients** – Hospitalization may provide an opportunity to start individuals with OUD on medication and engage them in care. Initiating MOUD during hospitalization appears to be associated with reduced illicit opioid use and greater adherence to treatment as compared with those who are not started on MOUD [27-29].

  Our preferred standard initiation regimen for buprenorphine in this circumstance is as follows:

  - Administer buprenorphine 4 mg sublingual
  - If ongoing symptoms of withdrawal persist after 45 minutes administer buprenorphine 4 mg sublingual
  - Administer additional buprenorphine 4 to 8 mg sublingual every six hours for ongoing withdrawal symptoms

  Most patients will not require more than 24 mg total daily dose of buprenorphine in a 24-hour period, although patients who have been using high potency illicit opioids (eg, fentanyl) may require up to 32 mg over 24 hours.

Benefits of using transmucosal buprenorphine — Transmucosal buprenorphine improves treatment retention, reduces opioid use, and is associated with decreased mortality in individuals with OUD [1]. As examples:

- In a meta-analysis of clinical trials, treatment retention was greater at low dose (2 to 6 mg; relative risk 1.5, 95% CI 1.2-1.9), medium doses (7 to 15 mg; relative risk 1.74, 95% CI 1.1-2.7), and high dose (≥16 mg; relative risk 1.82, 95% CI 1.2-2.9) of sublingual buprenorphine compared with placebo [1]. However, in the meta-analysis, only high-dose buprenorphine (≥16 mg) was more effective than placebo in suppressing illicit opioid use (standard mean difference -1.17, 95% CI -1.85 to -0.49). In another trial, individuals treated with buprenorphine (16 mg) or buprenorphine-naloxone (16 mg/4 mg) more frequently had negative urine opioid screening tests compared with those who received placebo (21, 18, and 6 percent respectively) [30].

- A retrospective study of administrative health datasets examined mortality in patients with OUD during periods when they were on buprenorphine-naloxone (13,190 person years of follow-up) and periods when they were off buprenorphine-naloxone (23,712 person years of follow-up) [31]. All-cause mortality was lower when patients were on buprenorphine-naloxone compared with periods when patients were off (standardized mortality ratio 3 versus 11). Mortality due to problematic drug use or accidental drug poisoning was also lower when patients were on buprenorphine rather than off. (See "Opioid use disorder: Treatment overview", section on 'Pharmacologic management'.)

Injectable buprenorphine — The long-acting injectable (LAI) formulations of buprenorphine are effective for the treatment of OUD [32-34]. We typically use these formulations to address limited adherence, misuse, or diversion of transmucosal buprenorphine. There are two US Food and Drug Administration (FDA)-approved products.

- **Buprenorphine XR (Sublocade)** – This is an LAI form of buprenorphine that is administered subcutaneously. It is used after a stabilization on transmucosal buprenorphine for a minimum of seven days.

  - **Initiating buprenorphine XR (Sublocade)** – This formulation is administered no more frequently than every 26 days and typically monthly [35]. The procedure for dose stabilization depends upon whether the patient has been on transmucosal buprenorphine for long-term management or for a few days. In either case, transition to Sublocade can occur directly.

    - For patients on long-term treatment with transmucosal buprenorphine (ie, months or years), the initial dose of Sublocade for the first month is 300 mg. The dose for the second month dose depends on the total daily dose of buprenorphine previously used. The second dose is 300 mg in individuals who were using greater than 20 mg/day transmucosal buprenorphine or in those with persistent craving or withdrawal symptoms. In individuals who were using 8 to 18 mg transmucosal buprenorphine per day, the second month injection may be 100 mg. In both cases, this is followed by 100 mg monthly maintenance doses.

    - For patients who have been on transmucosal buprenorphine for a relatively short period (at least seven days, but typically not for weeks), the first month and the second month doses are each 300 mg, and then subsequent doses are 100 mg.

    While the ultimate recommended maintenance dose is 100 mg, a maintenance dose of 300 mg monthly may be used if the benefits outweigh the risks. For example, if the patient has continued opioid use or symptoms of withdrawal on the 100 mg dose,

continuation on the 300 mg monthly dose may be indicated. In addition, situations (eg, extended travel) may arise during maintenance treatment in which a 300 mg dose may be administered to cover a two-month period. Once the situation has passed, the maintenance regimen should revert to 100 mg/month. Patients who are receiving 100 mg/month and then receive a 300 mg injection may experience sedation or other adverse effects due to the higher peak serum concentration.

- **Buprenorphine XR (Brixadi)** – This is an LAI form of buprenorphine that is also administered subcutaneously. Unlike Sublocade, a period of transmucosal stabilization is not necessary [36].

  - **Initiating buprenorphine XR (Brixadi)** – For persons not on transmucosal buprenorphine, a test dose of 4 mg of transmucosal buprenorphine should be given to ensure there is no precipitated withdrawal before giving the first subcutaneous injection. The weekly dose formulation should be used initially. Doses can be administered in the buttock, thigh, or abdomen, but then can be given in the upper arm after four weekly injections. Weekly and then monthly doses vary depending upon whether the patient has been treated with transmucosal buprenorphine, and if they have, their daily dose. The package insert provides guidance on the dosing and should be referenced when starting a patient on this formulation.

    A clinical trial found the buprenorphine XR (Brixadi) to have similar effect to daily, sublingual buprenorphine in response rates and having urine test results negative for illicit opioids [33].

- **Benefits of buprenorphine XR** – Individuals with moderate to severe OUD who are treated with buprenorphine XR are found to have higher abstinence rates than treatment with placebo. As examples:

  - In a multisite clinical trial of 202 patients with moderate to severe OUD individuals were randomly assigned to treatment with 300 mg injections monthly for six months versus 300 mg injection monthly for two months, followed by 100 mg injection monthly for four more months versus placebo [34]. Individuals treated with injectable buprenorphine XR maintained higher abstinence rates than those treated with placebo (opioid abstinence rates of 41.3 and 42.7 percent versus 5 percent for 300/300, 300/100, and placebo groups, respectively). The product was well tolerated and had a side effect profile similar to transmucosal buprenorphine.

  - In a separate follow-up observational study, 425 patients with OUD who had received up to 12 months of monthly buprenorphine XR injections as part of a clinical efficacy

trial were monitored [37]. Longer durations of treatment were associated with higher rates of sustained abstinence. Additionally, patients had sustained improvements in mood, pain, and health-related quality of life, as well as higher employment rates than at the time of pretrial screening.

- **Risk evaluation and mitigation strategy (REMS) program for buprenorphine XR** – In the United States, providing either form of buprenorphine XR (Sublocade or Brixadi) can only occur through certified health care settings and pharmacies, as a part of each medication's REMS program. There is a restricted distribution system for buprenorphine XR, and the medication is never given to patients for self-administration. Further information on the REMS program, including enrollment in the program, can be found on the website.

Adverse effects — Buprenorphine-related deaths in patients on maintenance therapy have occurred primarily when buprenorphine is taken in combination with other substances, especially benzodiazepines and/or alcohol [38,39] and with intravenous misuse of high doses of buprenorphine [40]. Death is caused by oversedation leading to respiratory depression and hypoxia. Buprenorphine has a lower potential for lethal overdose compared with methadone.

Dental problems including dental caries, abscesses, and damaged teeth, many of which have required extraction may be associated with the use of buprenorphine formulations dissolved in the mouth [41-43]. Patients who use oral dissolving buprenorphine should rinse around the teeth and gums with water once the film has completely dissolved. Individuals taking buprenorphine formulations should notify their dentist that they are taking the drug and follow up with routine scheduled dental care. The FDA has issued a safety advisory for this issue and will be mandating a related label change for buprenorphine.

Other adverse effects of buprenorphine include headache, nausea, constipation, pain, and sweating. While these can be distressing to patients, they are not uncommon symptoms experienced while using opioids. Adherence is relatively rarely disturbed by these effects.

Tapering buprenorphine — We support the strategy of continuing opioid agonist treatment indefinitely for individuals who have responded to treatment for OUD. However, when the decision is made to discontinue medication for OUD in individuals on buprenorphine, we taper over several months if possible.

- **Transmucosal buprenorphine** – We typically reduce the dose by 2 mg every one to two weeks. Based on clinical symptoms, such as the emergence of craving or withdrawal, we may slow down this process as the taper nears the end. If a more rapid taper is necessary (eg, prior to incarceration), the dose can be reduced by 2 mg every one to three days.

The relative efficacy of different buprenorphine tapering schedules has not been well studied, but available data suggest that slow, gradual tapers (eg, over months) are more effective and better tolerated than rapid tapers (eg, over days) [44].

We include the individual's primary clinician, program counselor (when the individual is in an opioid treatment program), and other supports (eg, family members with authorization) and employ shared decision-making in planning for taper off of any treatment for OUD. Clinicians without experience tapering a patient off of a maintenance medication would benefit from consultation with a clinician who has such experience.

If the individual becomes unstable with recurrent substance use, craving, withdrawal symptoms, or life stressors, the taper should be halted, and they should be encouraged to remain on medication until stability is again achieved.

- **Longer-acting formulation** – Individuals discontinuing buprenorphine XR after sustained use (ie, at least four to six months) may have detectable plasma and urine levels of buprenorphine for 12 months or longer [45]. Tapering off the LAI form could theoretically occur by simply stopping the administrations and allowing the gradual decrease in blood levels to occur over the subsequent weeks.

Regulation of buprenorphine in United States — Buprenorphine is classified as a schedule III controlled substance in the United States. To prescribe buprenorphine for patients with an OUD, clinicians had to apply for a federally required DATA Waiver (X-Waiver). However, in 2023 the Consolidated Appropriations Act removed this requirement. This allows clinicians with schedule III authority on their Drug Enforcement Administration registration to prescribe buprenorphine for opioid use disorder if permitted by applicable state law [46]. Induction may be accomplished in the clinician's office under observation or at the patient's home [47]. When on a stable dose, patients may receive a prescription for up to a one-month supply of medication with refills for up to six months, similar to other schedule III controlled substances. There are no longer any limitations in the number of patients any individual clinician can treat.

METHADONE: OPIOID AGONIST

Methadone treatment for opioid use disorder (OUD) is available by prescription and utilizes pharmacy-based dispensing in many countries including Australia, the United Kingdom, and Canada. In the United States, methadone is dispensed through a federally regulated clinic system [48,49]. (See 'Regulation of methadone in United States' below.)

Methadone, a long-acting opioid agonist, binds to and occupies mu-opioid receptors, preventing withdrawal symptoms for 24 hours or longer. Methadone reduces craving for opioids, and, by maintaining high levels of opioid tolerance, reduces the euphoric effects of subsequent illicit opioid use. Although individuals treated with methadone are physically dependent upon the medications, they do not typically have the pattern and severity of problematic behaviors associated with use and misuse of heroin or pharmaceutical opioids including fentanyl and are often able to return to a productive lifestyle [7,8].

Methadone formulations — Methadone is typically given as a liquid, often diluted with juice or water or artificially colored water. (Each patient receives a full cup of uniformly colored liquid, regardless of the dose of methadone, to reduce anxiety among patients about differences in dose. The dilution and coloring are also intended to reduce the likelihood of a patient injecting "take-home" methadone.) Methadone is available in a tablet form, as well as a dissolvable diskette, and there has been some increase in the use of these forms by opioid treatment programs in the United States during the coronavirus disease 2019 (COVID-19) pandemic.

While different formulations of methadone are available, our preference is to avoid switching formulations if possible. Based upon reports from clinicians and patients, Health Canada issued a safety alert that switching from one liquid formulation of methadone to another liquid formulation at the same dose may elicit withdrawal symptoms, which can lead to nonadherence and problematic substance use [50].

Prior to starting methadone — Prior to beginning treatment with methadone we assess for potential drug-drug interactions that may help to inform dosing, and the risk of other medical comorbidities relevant to methadone's use:

- Drug-drug interactions may occur with several commonly used medications (anticonvulsants, antibiotics, antidepressants, antiretrovirals) (table 2). (See 'Other adverse effects and considerations' below.)
- Methadone may be associated with QTc prolongation. For the majority of patients, an electrocardiogram (ECG) prior to beginning methadone is not indicated. For individuals with a history of syncope, arrhythmia, structural heart disease, prolonged QTc, or family history of prolonged QTc, an ECG should be obtained. Additionally, we get an ECG prior to treatment with methadone in individuals already being treated with medications that can prolong QTc.
    - For QTc interval >450 msec but <500 msec – We start methadone and monitor the ECG 30 days after starting and then annually.

- For QTc interval ≥500 msec – We prefer not to start methadone prior to cardiology consultation. We closely weigh the benefits of treatment with methadone with the risks of arrhythmia. If methadone is started, we monitor the ECG 30 days after starting the medication then annually.

As there is no compelling research evidence to base a decision on whether to obtain an ECG prior to the start of methadone treatment [51-53], we base our decision on clinical experience.

Initial dose and titration — The typical initial dose of methadone for OUD is 20 to 30 mg in a single dose. The maximum initial dose allowed by most federal regulations or national guidelines is 30 mg [54,55]; however, an additional 10 mg may be administered a few hours later if the individual has significant withdrawal symptoms. The total dose for the first day should not exceed 40 mg. Observation at three hours after the first dose is recommended, if possible, to monitor for signs of toxicity or withdrawal.

The initial dose of methadone maintenance treatment varies based upon the time of the last opioid use, the amount used, and whether the patient has developed a reduction in tolerance to opioids (eg, patients who were recently released from incarceration or hospitalization may have significantly reduced tolerance).

Methadone is titrated in 5 to 10 mg increments no more frequently than every two to three days over several weeks until an initial dose in the range of 60 to 80 mg total daily dose is reached. Gradual adjustment allows methadone to reach a pharmacologic steady state to match the patient's level of opioid tolerance and avoid intoxication or oversedation. Additionally it may help to avoid the rare but possible event of iatrogenic overdose. If excessive opioid agonist effects (eg, sedation) occur, further dose increases are halted. If needed, we titrate beyond 60 to 80 mg per day slowly (eg, 10 mg per week) provided patients do not have intolerable side effects. The rate of titration and eventual dose is based upon the intensity of cravings, the presence of opioid withdrawal symptoms (which are assessed daily) and the cessation of illicit opioid use (as determined by patient reports and urine testing).

Maintenance — Methadone dosing for maintenance treatment varies [56]. Specifying the dose can be difficult, in part as the dose does not correlate well with blood levels. A relatively low dose of methadone (eg, 20 to 30 mg per day) attenuates acute opioid withdrawal but is usually not as effective as higher doses at suppressing craving and blocking the effects of other opioids, such as heroin. Higher doses (ie, 80 to 100 mg/day) are not overly sedating following the development of tolerance. Doses of up to 150 mg per day are not uncommonly used and higher levels of physical dependence associated with fentanyl use may require higher doses of methadone.

Several randomized trials have found that patients on higher doses of methadone (80 to 100 mg/day) have higher retention rates and lower illicit use of opioids than lower methadone doses [6,57,58].

In the United States, patients who have reached a steady maintenance dose, take-home administration of methadone is a consideration. Eligibility for take-home doses is usually based on adherence to program requirements for counseling and abstinence from illicit drugs (based on urine toxicology testing), as well as absence of recent criminal activity and capacity to store the take-home doses safely in the home environment.

Benefits of methadone treatment — Methadone treatment is associated with decreased all-cause mortality from OUD, reduced risk of mortality from overdose (primarily heroin overdose), increased likelihood of remaining in treatment and reduced opioid use compared with those receiving placebo or nonmedication treatment [4,31,59,60].

As examples:

- In a meta-analysis of 11 studies including 1969 individuals with the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) opioid dependence who were treated with methadone maintenance, individuals treated with methadone were more likely to remain in treatment and to reduce opioid use (relative risk 0.66, 95% CI 0.56-0.78) compared with individuals on placebo or nonmedication treatment [4].

- A retrospective study of administrative health datasets examined mortality in patients with OUD during periods when patients were on methadone (188,113 person years of follow-up) and periods when patients were off methadone (174,431 person years of follow-up) [31]. All-cause mortality was lower when patients were on methadone compared with periods when patients were off (standardized mortality ratio 4.7 versus 9.5). Mortality due to problematic drug use or accidental drug poisoning was also lower when patients were on treatment rather than off. Another observational study suggested a 70 percent reduction in the risk of mortality with methadone maintenance, attributable mainly to prevention of opioid (ie, heroin) overdose [60].

Furthermore, methadone maintenance treatment can have beneficial effects beyond the use of opioids. Methadone treatment has been associated with reductions in the spread of human immunodeficiency virus [61-63], and in some studies, with reduced criminal behavior [4,64].

Tapering off of methadone — We support the strategy of continuing opioid agonist treatment indefinitely for individuals who have responded to treatment for OUD. However, when the

decision is made to discontinue medication for OUD in individuals on methadone, we taper slowly (over months) and gradually (eg, dose decreases of up to 5 mg/week with smaller dose decreases as the taper nears the end). We allow and encourage the patient to pause the taper if instability such as withdrawal symptoms occurs.

Adverse effects — Adverse effects of methadone therapy include constipation, drowsiness, diaphoresis, peripheral edema, and rarely cardiac arrhythmia [65,66].

Prolonged QTc and cardiac arrhythmias — We check ECG 30 days after starting methadone and then annually thereafter in individuals at risk for prolonged QTc. This includes individuals with a history of syncope, arrhythmia, structural heart disease, prolonged QTc (>450 msec), family history of prolonged QTc or in individuals on other medications that can prolong QTc. Our response to the ECG findings are as follows:

- For QTc interval >450 msec but <500 msec – We continue treatment and monitor the ECG annually.
- For QTc interval ≥500 msec – We prefer to discontinue methadone; however, we closely weigh the benefits of treatment with methadone with the risks of arrhythmia. We often lower the dose of methadone (if clinically reasonable) while addressing other causative factors such as hypokalemia or other medications that may cause prolonged QTc. However, we typically consult with a cardiologist prior to making medication adjustments.

Studies have noted a significant but weak relationship between the methadone dose and the degree of QTc prolongation at doses of up to 300 mg/day [67-70]. Additionally, methadone use in both therapeutic dose and overdose has been associated with QTc interval prolongation and torsades de pointes, which in some cases has been fatal [71]. However, while the risk of QTc prolongation in methadone treated patients is controversial, concern regarding the proarrhythmic potential of methadone prompted a clinician safety alert from the US Food and Drug Administration.

Some research suggests that substitution of (R,S)-methadone with (R)-methadone reduces the methadone-induced prolonged QTc interval among individuals with OUD [72]. Further work is needed to confirm this finding. The (R)-methadone formulation is available in the European Union and is widely used in Germany, but is not available for clinical use in the United States. The use of a pure (R)-formulation of methadone also results in lower effective doses, but its cost is up to 20 percent higher than the racemic formulation [73].

The associated table lists causes of prolonged QTc (table 3). Drug-induced QTc prolongation is discussed in detail separately. (See "Acquired long QT syndrome: Definitions,

pathophysiology, and causes".)

Other adverse effects and considerations — Other adverse effects and drug-drug interactions include:

- **Hyperalgesia** – Chronic use of methadone and other opioid agonists may result in an increased sensitivity to pain, which may develop within a month of initiating chronic opioid therapy [74-76]. A study of patients in methadone treatment programs found chronic severe pain was reported by 37 percent of the patients, and 65 percent of those with pain experienced a significant impact on physical and psychosocial functioning [76]. Patients in methadone treatment may have a history of physical trauma resulting in chronic pain, but may also have increased sensitivity to pain related to chronic opioid use [77].

- **Overdose** – As a full agonist, methadone has a greater potential for lethal overdose compared with buprenorphine, a partial mu-opioid agonist. Death during induction into methadone maintenance treatment has been reported in a series of cases from New South Wales, Australia [78-80]. The overall mortality rate during methadone maintenance induction was 7.1 deaths per 10,000 inductions [80]. Concurrent benzodiazepine use was a significant risk factor contributing to likelihood of death both in methadone maintenance patients and in patients taking methadone for chronic pain [81].

- **Reduced libido and erectile dysfunction** – Reduced libido and erectile dysfunction are common among heroin users and those in treatment for OUD. Methadone use is believed to contribute to erectile dysfunction, possibly through reduction in serum testosterone levels; however, psychological and social factors are also associated with erectile dysfunction [82,83]. These other factors should be considered before attributing erectile dysfunction solely to methadone treatment.

- **Drug interactions and metabolism** – Methadone has a number of drug interactions based on metabolism by the cytochrome P450 isoenzyme system, specifically CYP 3A4, 2D6, and 2B6 (table 2) [84,85]. Starting or stopping medications that interact with these enzymes can affect serum methadone levels. This may result in opioid withdrawal or intoxication.

  Daily methadone dose may need adjustment to prevent complications from these interactions. For example, individuals who concurrently take benzodiazepines or use alcohol may be more likely to become sedated from methadone and should be evaluated for the risk of respiratory depression. In these cases, dose of medications should be adjusted accordingly.

Regulation of methadone in United States — Methadone is regulated in many countries including the United States, where it is classified as a schedule II drug. Many of the regulations on methadone's use are aimed at preventing diversion of medication and reducing the risk of overdose. Only licensed opioid treatment programs or licensed inpatient hospital units in the United States are permitted to order and dispense methadone for withdrawal or long-term treatment of an OUD [86]. Exceptions to this restriction include:

- Patients already receiving methadone from a licensed program may continue to receive the medication during inpatient hospitalization to treat OUD or other conditions, such as pain.

- Any clinician or other licensed prescriber may administer methadone (or any other opioid) to treat a patient with acute opioid withdrawal for up to three days while arranging for more definitive treatment, provided they follow federal regulations (21 CFR 1306.07(b)). The intent is to relieve suffering and prevent withdrawal that would complicate the primary medical or surgical condition. While methadone may be administered to a patient during the 72-hour period, it may not be dispensed or prescribed for unsupervised use.

To be eligible for methadone maintenance in the United States under federal guidelines, a prospective patient must have [86]:

- Documentation of the presence of an OUD for at least one year of continuous use. Exceptions to this criterion include:

  - Patients who have been on methadone maintenance within the past two years do not need to demonstrate current physical dependence or a current OUD if the program clinician documents a likelihood of an imminent relapse to opioid use.

  - Patients recently released from incarceration or hospitalization do not need to show current physiologic dependence or OUD but are required to have a history of an OUD and have a clinician document a likelihood of relapse to opioid use and physiologic dependence.

  - Pregnant women are eligible for methadone maintenance even if an OUD has been present for less than one year.

- Age 18 years or older – Younger individuals are eligible for treatment with the consent of a parent, guardian, or designated responsible adult if they have current opioid physical dependence and have at least two previous attempts at detoxification or psychosocial substance abuse treatment.

Licensed United States outpatient treatment programs are required to provide counseling and social services in addition to methadone. Patients are required to attend individual counseling as clinically indicated. (See "Opioid use disorder: Psychosocial management".)

In addition to federal regulations, many states in the United States have imposed additional restrictions on methadone for use in the treatment of an OUD.

Switching between agonist treatments — Individuals with physiologic opioid dependence who are transitioned directly from methadone maintenance to buprenorphine may experience acute precipitated opioid withdrawal syndrome [87,88]. In these cases, we often use low-dose buprenorphine induction. (See 'Alternative induction methods for specific circumstances' above.)

For individuals with physiologic opioid dependence who have a poor response or unacceptable side effects to buprenorphine, this medication can be discontinued and methadone started immediately.

NALTREXONE: OPIOID ANTAGONIST

Naltrexone, an opioid antagonist, blocks the effects of opioids if they are used, thus preventing the user from experiencing opioid intoxication or physiologic dependence with subsequent use and thus reinforces abstinence.

Prior to treatment with opioid antagonist — Naltrexone should be used only after completion of a medically supervised withdrawal from opioids because it can precipitate immediate withdrawal symptoms. Initiation of naltrexone should be medically supervised.

In some cases, a naloxone challenge test is useful to ensure that the patient has completed withdrawal from opioids and is no longer physically dependent on this class of drugs. If there are reasons to suspect that the person has not had a sufficient period of opioid abstinence (eg, an outpatient who has attempted to abstain from opioids on their own for several days), then a naloxone challenge test should be undertaken.

However, in our experience most patients are forthright about their use when it is explained that there is a risk of precipitated withdrawal with naltrexone dosing if they have continued opioid use. When needed, the naloxone challenge test is done as follows:

- The patient should be totally free of spontaneous opioid withdrawal signs and symptoms at the start of the naloxone challenge session.

- Baseline vital signs are obtained, and naloxone is then administered parenterally (subcutaneously, intramuscularly [IM], or intravenously) up to a total dose of 0.8 mg.

- The patient is observed for up to one hour, and a validated measure for assessing opioid withdrawal, such as the Clinical Opiate Withdrawal Scale can be helpful to use.

If any symptoms or signs of opioid withdrawal emerge, or if pulse rate or blood pressure increases, administration of naltrexone should be postponed for another 24 hours. Since naloxone has a short half-life, any withdrawal precipitated by naloxone typically will resolve within one to two hours of administration or less.

Long-acting injectable naltrexone — Our preference is to treat opioid use disorder (OUD) with long-acting injectable (LAI; or extended-release) naltrexone rather than oral naltrexone. LAI naltrexone is given every four weeks by deep IM injection in the gluteal muscle at a set dose of 380 mg per injection. It should be administered in alternating buttocks each month. The medication is started 7 to 10 days after last opioid use unless a naloxone challenge test is conducted and confirms the safety of starting oral naltrexone sooner.

The American Society of Addiction Medicine has suggested that in cases of breakthrough cravings LAI naltrexone may be given every three weeks. However, there are currently no studies to support this more frequent dosing, and this is not our routine practice.

- **Benefits of LAI naltrexone** – In randomized trials, LAI naltrexone is more effective than placebo for opioid dependence [2,89-91]. However, the transition to LAI naltrexone may be a challenge for some individuals; additionally, trials of LAI naltrexone have been limited by high dropout rates [2,89]. For example:

  - In a trial, 250 individuals with DSM-IV opioid dependence were randomized to receive 24 weeks of injectable depot formulation of naltrexone versus placebo [2]. The median proportion of weeks of confirmed abstinence was greater in the actively treated group compared with the placebo group (90 versus 35 percent). However, these findings exclude 47 percent of the patients who did not complete the study.

  - In a trial, 308 individuals in the criminal justice system were randomly assigned to LAI naltrexone versus treatment as usual (brief counseling and referral to community treatment program) for a period of 24 weeks [3]. Individuals in the treatment group had a longer median time to relapse (10.5 versus 5 weeks), a lower rate of relapse (43 versus 64 percent), and higher rate of opioid negative urine samples (74 versus 56 percent) versus control group. However, at 78-week follow-up, rates of opioid-negative urine samples were equal (46 percent in each group).

- **Injection site reaction** – Naltrexone via IM injection may cause injection site reaction consisting of pain, tenderness, and swelling at the injection site. In some cases, abscess, cellulitis, and necrosis have been reported. While treatment for such reactions is generally supportive, if symptoms appear to be worsening after seven days, further evaluation with a surgical specialist is warranted.

Oral naltrexone — We typically begin oral naltrexone at 25 mg per day for the first two to three days before increasing to 50 mg per day. The medication is started 7 to 10 days after last opioid use unless a naloxone challenge test is conducted and confirms the safety of starting oral naltrexone sooner. (See 'Prior to treatment with opioid antagonist' above.)

- **Benefits of oral naltrexone** – Efficacy of oral naltrexone for sustained abstinence in treatment of individuals with opioid dependence is limited. A meta-analysis of 1158 participants in 13 randomized trials compared oral naltrexone maintenance treatment with either placebo or no medication for opioid dependence [92]. Primary outcomes such as sustained abstinence were similar between active and control groups. The findings from these trials were limited by poor adherence and high dropout rates. However, oral naltrexone was more effective than placebo in sustaining abstinence in three trials where patients were monitored for daily adherence by a close relative [92].

- **Adverse effects and subsequent considerations** – Oral naltrexone has few side effects or adverse effects. Occasionally patients will report nausea, headache, dizziness, or fatigue. More severe adverse effects include liver damage, but this is very rare (seen with supratherapeutic doses) and has always resolved with discontinuation of naltrexone.

  Patients who discontinue antagonist therapy and resume opioid use should be made aware of the risks associated with an opioid overdose and especially the increased risk of death. This is due to the loss of tolerance to opioids and a resulting misjudgment of dose at the time of relapse [93].

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Opioid use disorder and withdrawal".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, “The Basics” and “Beyond the Basics.” The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on “patient info” and the keyword(s) of interest.)

- Basics topics (see "Patient education: Prescription drug misuse (The Basics)" and "Patient education: Opioid use disorder (The Basics)")

SUMMARY AND RECOMMENDATIONS

- **Our approach** – We prefer to treat all individuals with opioid use disorder (OUD) with medication for OUD (MOUD) and psychotherapy. MOUD reinforces abstinence and improves treatment retention. Our approach to selecting treatments including medication and psychotherapy is discussed elsewhere (algorithm 1). (See "Opioid use disorder: Treatment overview".)

- **Opioid agonists** – Opioid agonists (eg, methadone and buprenorphine) suppress craving and withdrawal symptoms while blocking the acute effects of other opioids. Although individuals treated with opioid agonists are physically dependent upon the medications, they do not typically have the severity of problematic behaviors associated with illicit use or misuse of opioids. (See 'Buprenorphine: Opioid agonist' above and 'Methadone: Opioid agonist' above.)

- **Buprenorphine** – Buprenorphine is most often given transmucosally as a combination preparation with naloxone to prevent diversion of the product. It is also available as a longer-acting injectable formulation. In most formulations, the dose depends on the duration and dose of prior transmucosal use. (See 'Transmucosal formulations' above and 'Injectable buprenorphine' above.)

  - For most individuals, we use a standard induction to initiate transmucosal buprenorphine. We wait until the individual shows signs of early withdrawal and then

start 4 mg of buprenorphine and gradually titrate up until withdrawal symptoms have resolved. (See 'Standard induction' above.)

- For individuals who present for induction without withdrawal symptoms, who have high levels of physical dependence, or who are transitioning from methadone, we suggest a low-dose protocol, in which a lower dose than that used for standard induction is administered more frequently (**Grade 2C**). (See 'Alternative induction methods for specific circumstances' above.)

- **Methadone** – Methadone, a long-acting opioid agonist, binds to mu-opioid receptors, preventing withdrawal symptoms for 24 hours or more. (See 'Methadone: Opioid agonist' above.)

  - In the United States, administration of methadone takes places in an opioid treatment program. Take-home doses of methadone may be available based on program requirements. (See 'Regulation of methadone in United States' above.)

  - Methadone carries a risk for lethal overdose. Other adverse effects include QTc prolongation, drug-drug interactions, and hyperalgesia. (See 'Adverse effects' above.)

- **Opioid antagonists** – Naltrexone, an opioid antagonist, prevents the user from experiencing opioid intoxication or physiologic dependence, thereby reinforcing abstinence. Naltrexone can precipitate withdrawal in individuals with physiologic opioid dependence and should be used only after completion of medically supervised withdrawal. (See 'Naltrexone: Opioid antagonist' above.)

  - Naltrexone is available in oral and long-acting injectable (LAI) formulation. We typically use the LAI naltrexone formulation when addressing limited adherence. (See 'Long-acting injectable naltrexone' above.)

  - Naltrexone LAI may cause an injection site reaction (ie, pain, swelling, abscess, cellulitis, necrosis). Treatment for injection site reactions is generally supportive; however, worsening symptoms after seven days warrants evaluation with a surgical specialist. (See 'Naltrexone: Opioid antagonist' above.)

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