Opioid use disorder: Treatment overview

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INTRODUCTION

Most patients with opioid use disorder (OUD), including those who have already achieved abstinence through medically supervised withdrawal or other means, may require long-term treatment to prevent returning to use.

First-line treatment for patients with OUD most commonly consists of pharmacotherapy with an opioid agonist or antagonist and adjunct psychosocial treatment. However, due to patient preference or availability, it may be necessary to treat individuals with either medication or psychosocial treatment alone.

Our approach to selecting treatment for OUD is described in this topic (algorithm 1). The epidemiology, pharmacology, clinical manifestations, course, assessment, and diagnosis of OUD are reviewed separately. Medication administration and dosing and psychosocial treatments for OUD are discussed in detail elsewhere. Misuse of prescribed medications including opioids is also discussed separately.

- (See "Opioid use disorder: Pharmacologic management".)
- (See "Opioid use disorder: Psychosocial management".)
- (See "Opioid use disorder: Epidemiology, clinical features, health consequences, screening, and assessment".)
- (See "Opioid withdrawal: Medically supervised withdrawal during treatment for opioid use disorder".)

- (See "Prescription drug misuse: Epidemiology, prevention, identification, and management".)

BEFORE INITIATING TREATMENT

Shared decision-making — Selecting treatment for opioid use disorder (OUD) should be made on the basis of shared decision-making between the clinician and the patient (and may also include family members). Although we feel strongly about providing pharmacotherapy in the treatment of OUD, we acknowledge that many patients may decline this option. Educating the individual about potential advantages and disadvantages of treatment options, including the use of medications, is an important part of the treatment planning that should be done prior to beginning treatment.

Several trials have demonstrated the importance of shared decision-making in treatment decisions. In a systematic review of 25 trials including 8729 individuals with substance use disorder, 44 percent of patients approved of self-selection of treatment goals, 46 percent preferred shared selection, and 11 percent preferred therapist-selection of treatment goals [1]. When individuals were matched to their preferred treatment, substance use outcomes (eg, reduction of consumption, severity of dependence, or abstinence) were better for some substances than among those who were unmatched to their preferred treatment. Additionally, in a trial of 3103 patients with substance use disorder who were seeking treatment (a proportion of whom primarily used heroin), drug use outcomes at one-year follow-up were higher in individuals whose patient-reported needs were matched to services [2].

Evaluate severity of opioid use disorder — We base our treatment of OUD primarily on the presence or absence of physical dependence (eg, withdrawal symptoms with discontinuation). For the purpose of deciding among treatment options, we consider individuals with physical dependence to have moderate to severe OUD whereas those without physical dependence we consider to have mild OUD. In clinical practice, we find it highly unusual for an individual to meet the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria for moderate to severe opioid withdrawal without physical dependence. Our distinction is for treatment purposes only and contrasts with the DSM-5 criteria which categorizes severity based on the number of criteria met (table 1). (See "Opioid use disorder: Epidemiology, clinical features, health consequences, screening, and assessment", section on 'Diagnosis'.)

Most clinical trials on the efficacy of treatments for OUD studied patients with a Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) diagnosis of opioid dependence.

Applying these findings to patients diagnosed using the DSM-5 criteria is imprecise, but the most closely comparable group of patients is those with OUD, moderate to severe subtype (ie, patients with four or more diagnostic criteria within a 12-month period).

Education and overdose prevention — We recommend providing overdose prevention education and naloxone distribution as an initial step and as part of an ongoing discussion in the context of clinical encounters. While this is important in all individuals with OUD, individuals who are not undergoing treatment using medication for OUD (MOUD) are at greater risk for overdose than individuals using MOUD. (See "Prevention of lethal opioid overdose in the community".)

INITIAL TREATMENT

Patients with physical dependence (moderate to severe disorder) — For most individuals with moderate to severe opioid use disorder (OUD), we recommend first-line treatment with pharmacologic management. We also recommend augmentation with psychosocial treatment. Clinical trials and studies have shown that medication for OUD (MOUD) reinforces abstinence, improves treatment retention, and is associated with a reduction in mortality including deaths by suicide during stable treatment periods [3-7]. These data are discussed in detail elsewhere. (See "Opioid use disorder: Pharmacologic management".)

Pharmacologic management — For initial treatment of moderate to severe OUD, we typically prefer an opioid agonist (buprenorphine or methadone) rather than an opioid antagonist (ie, naltrexone). Of the agonists, we typically prefer buprenorphine over methadone; however, in individuals with high tolerance (as evidenced by the need to use high doses to achieve the desired effect), methadone is our preferred choice. In individuals who cannot or will not take agonist treatment, naltrexone is a reasonable alternative; however, individuals who will be treated with naltrexone need medically supervised withdrawal before initiation of an antagonist.

An algorithm describes our approach to selecting MOUD (algorithm 1). (See "Opioid use disorder: Pharmacologic management".)

Dosing and initiation of opioid agonists and antagonists are discussed elsewhere. (See "Opioid use disorder: Pharmacologic management", section on 'Naltrexone: Opioid antagonist' and "Opioid use disorder: Pharmacologic management", section on 'Methadone: Opioid agonist'.)

Preference for agonist over antagonist treatment — As there are few studies comparing treatment options for OUD [3,8], our preference for agonist treatment (ie,

buprenorphine or methadone) over naltrexone (algorithm 1) is based on the following:

- **Decreased mortality associated with opioid agonist treatment** – Observational data have shown decreased mortality with opioid agonist treatment for individuals with OUD versus individuals not in treatment [9-12]. Preliminary evidence indicates that naltrexone may have similar positive effects on mortality; however, more data are required to confirm this effect [13]. Examples of the benefits of agonist treatment of OUD on mortality include:

  - In a meta-analysis including 30 observational studies and over 562,000 individuals with OUD, treatment with opioid agonists was associated with a lower risk of all-cause mortality compared with no opioid agonist use (relative risk 0.47, 95% CI 0.42-0.53) [10]. Additionally, while receiving opioid agonist treatment, individuals with OUD were at lower risk of all injury and poisoning, suicide, cancer, alcohol-related mortality, and cardiovascular-related mortality.

  - In a meta-analysis of observational studies that included 122,885 individuals treated with methadone for up to 14 years and 15,831 individuals treated with buprenorphine for up to 4.5 years [14], pooled all-cause mortality rates were 11.3 and 36.1 per 1000 person years with versus without methadone (adjusted relative risk 3.2, 95% CI 2.65-3.86) and 4.3 and 9.5 per 1000 person years with versus without buprenorphine (adjusted relative risk 2.2, 95% CI 1.34-3.61).

  Additionally, opioid agonists appear to be associated with decreased all-cause and opioid-related mortality, compared with no medication treatment, in individuals who have survived a past opioid overdose [15].

- **Need to successfully complete opioid withdrawal prior to treatment with an opioid antagonist (naltrexone)** – Because opioid antagonists precipitate withdrawal in individuals actively using opioids, medically supervised withdrawal is necessary prior to initiation of an antagonist. Medically supervised withdrawal may be particularly difficult in an outpatient setting, making transition to an antagonist less practical than an agonist, which can be started in individuals actively using opioids. However, for those who can complete withdrawal successfully, effectiveness of long-acting injectable (LAI) naltrexone can be similar to that of buprenorphine in preventing return to use [8].

Preference for buprenorphine over methadone — Of the agonists, we prefer initial treatment with buprenorphine over methadone for most individuals with moderate to severe OUD (algorithm 1). While methadone may be more appropriate for individuals with higher levels of physical dependence or in individuals with poor response to, or prior misuse/diversion of buprenorphine, buprenorphine has several distinct advantages:

- **Lower risk of death with overdose** – There may be higher lethality with methadone overdose than with buprenorphine overdose if the medication is diverted and misused [16,17]. Buprenorphine, as a partial opioid agonist, has a much lower potential for causing respiratory depression. Methadone doses used for OUD usually exceed the lethal dose (50 mg) for opioid-naive adults, while the typical buprenorphine dose (8 to 16 mg/day) is well below this threshold. In a nonrandomized, retrospective study of 16,434 individuals with diagnosis of opioid dependence and treated with methadone or buprenorphine, the overall risk of an overdose death was lower for those treated with buprenorphine [17].

- **Accessibility** – There are large differences in the accessibility of buprenorphine and methadone in the European Union due to historic, economic, regulatory, and legal factors. Where available, these medications are prescribed on an outpatient basis at a specialized treatment center or primary health care settings, or primarily in Western Europe in low-threshold agencies [18]. In the United States, buprenorphine can be prescribed in a private office setting whereas methadone initially requires daily visits to a licensed opioid treatment program (OTP), with the caveat that OTPs can initially provide one dose to take at home per week. If needed, buprenorphine can also be administered through OTPs. (See 'Regulation in the United States' below.)

- **Drug interactions** – Buprenorphine may be associated with fewer drug-drug interactions than methadone.

While studies comparing buprenorphine and methadone for maintenance treatment of OUD appear to show that buprenorphine is slightly less effective than methadone in its capacity to retain patients in treatment at flexible or low doses, they appear to be equally effective in treatment retention and suppression of illicit opioid use at medium or high doses [3]. However, data supporting outcomes such as treatment retention or suppression of opioid use vary [3,19]. As examples:

- In a meta-analysis of randomized (n = 32) and observational (n = 69) studies comparing buprenorphine and methadone treatment for OUD, methadone had greater retention in treatment at all points measured (eg, 3, 6, 9, 12, and 24 months) after a one-month timepoint [20]. For example, at six-month follow-up, the pooled effect favored methadone in randomized trials (16 studies, n = 3252; odds ratio 0.76, 95% CI 0.67-0.85) and observational studies (21 studies, n = 155111; odds ratio 0.77, 95% CI 0.68-0.86).

- In a meta-analysis comparing methadone with buprenorphine in maintenance treatment of individuals with DSM-IV opioid dependence, buprenorphine retained fewer individuals in treatment when given in flexible doses (five studies, 788 participants; relative risk 0.83,

95% CI 0.72-0.95) or at low fixed dose (buprenorphine 2 to 6 mg, methadone ≤40 mg, three studies, 253 participants; relative risk 0.67, 95% CI 0.52-0.87) [3]. However, at medium doses (buprenorphine 7 to 15 mg; methadone 40 to 85 mg) the two medications were equally as effective in treatment retention (seven studies, 780 individuals; relative risk 0.87, 95% CI 0.69-1.10) and suppression of opioid use as measured by urinalysis (four studies, 476 participants; standardized mean difference 0.25, 95% CI -0.08 to 0.58). Similarly, at higher doses of buprenorphine (>16 mg) and higher dose methadone (≥85 mg), there was no difference in treatment retention (relative risk 0.79, 95% CI 0.2-3.16) or suppression of self-reported heroin use (standardized mean difference -0.73, 95% CI -1.08 to -0.37).

- In contrast, in a retrospective study 504 individuals with opioid dependence methadone (mean 80 mg/day) were associated with longer opioid abstinence (mean 7 versus 5.4 months) and retention in treatment (mean 9.4 versus 8.6 months) compared with buprenorphine (mean 16 mg/day) [21].

Adjunctive psychosocial intervention — We suggest adjunctive psychosocial intervention for all individuals being treated for OUD, but appreciate that some patients decline it. We do not require participation to continue MOUD therapy. Participating in adjunctive psychosocial services may be more strongly recommended when only a partial response is obtained from medication. Our approach to selecting psychosocial interventions and psychotherapy for OUD is discussed elsewhere. (See "Opioid use disorder: Psychosocial management", section on 'Selecting psychotherapy'.)

Efficacy for augmentation of pharmacologic treatment with psychosocial treatment for OUD is mixed [22-28]. While in some trials important outcomes such as lower rate of return to use or greater adherence to treatment appear to be associated with psychosocial intervention, interpretations are difficult due to variability in methods and outcomes across studies. Typical research outcome measures, such as amount of illicit opioid use or retention in treatment, may not always capture components of recovery that are positively affected by psychosocial support. These components may ultimately improve the patient's overall quality of life.

Some studies show improved treatment retention and abstinence rates with psychosocial intervention:

- In one study, 273 individuals with ongoing opioid and/or cocaine use while on an opioid agonist (buprenorphine or methadone) were randomly assigned to a "personalized psychosocial intervention" (PSI), a weekly treatment comprised of behavioral approaches (ie, cognitive-behavioral therapy [CBT], contingency management), 12-step facilitation and

family involvement, or treatment as usual [29]. Results indicated a higher percentage of abstinence from opioids and cocaine in the PSI group versus in the treatment-as-usual group (16 versus 7 percent, respectively). The PSI group also demonstrated more opioid and crack cocaine abstinent days than did the treatment-as-usual group [29].

- In another study, 94 individuals with OUD starting buprenorphine were randomly assigned to treatment in a manualized model with weekly CBT groups versus weekly supportive counseling at an OTP versus brief counseling from a primary care provider [30]. At 20-week follow-up, the percentage of individuals continuing in treatment was higher in the manualized model versus supportive treatment at OTP or brief counseling (52 versus 33 versus 21 percent respectively). [30].

  However, other studies do not show a difference in some important outcomes [28,31]. For example, in a systematic review of 20 studies including over 3200 individuals with OUD, the addition of adjunctive interventions (eg, primarily psychosocial interventions) to standard medical management with buprenorphine did not improve substance use outcomes (eg, abstinence, treatment retention) [31].

Other evidence suggests that patients receiving MOUD who are given a choice about counseling will voluntarily attend counseling about as often as those for whom counseling is required, demonstrating that patients may value the option of counseling when empowered to choose it themselves [32].

Patients without physical dependence (mild disorder) — For individuals with mild OUD, we suggest pharmacotherapy with an opioid antagonist (algorithm 1); we also augment with psychosocial treatment. For opioid antagonist therapy, we suggest LAI naltrexone (administered monthly); however, oral naltrexone (administered daily, optimally under supervision) is a reasonable alternative for highly motivated patients who refuse injections or have good external support.

Mild OUD has not been well studied; almost all trials of OUD treatment included only patients with a moderate to severe OUD. Treatment decisions for mild OUD are based upon our clinical experience.

Naltrexone as the initial treatment choice for mild OUD has at least three advantages compared with opioid agonists:

- Naltrexone effectively blocks the mu-opioid receptor, so if illicit opioids are used, the patient gets no effect and no euphoria, whereas some euphoria is possible if a higher dose of an illicit opioid is used by patients on buprenorphine or methadone.

- Naltrexone, unlike methadone and buprenorphine, does not cause physiologic dependence or a withdrawal syndrome when it is stopped, so for patients with mild OUD, naltrexone does not risk creating physiologic dependence when none currently exists.

- Naltrexone can be easily switched to methadone or buprenorphine if the individual has unacceptable side effects. However, switching from either of those medications to naltrexone is challenging because of the need to undergo 7 to 10 days of full withdrawal from those medications to avoid causing precipitated withdrawal when naltrexone is started.

LAI naltrexone has been found to be more effective than placebo for opioid dependence in randomized trials [5,33-35]. Oral naltrexone has been found to be effective compared with placebo when adherence is enforced [36]. In a head-to-head trial, LAI naltrexone outperformed oral naltrexone for treatment retention. Further information on the efficacy of naltrexone for OUD compared with placebo, its pharmacology, adverse effects, and administration are reviewed separately [37]. (See "Opioid use disorder: Pharmacologic management", section on 'Naltrexone: Opioid antagonist'.)

Individuals who decline medication for opioid use disorder — We do not suggest psychosocial treatment alone as the first-line treatment of OUD, especially if it is of moderate or severe severity. Evidence is insufficient to determine whether psychosocial treatment alone is effective in treating OUD [38].

However, we occasionally use psychosocial treatment alone in mild OUD if the individual has a history of prior sustained response, is highly motivated for treatment, and has good premorbid functioning including strong supports. Additionally, we would use it if the individual refuses medication treatment and prefers psychosocial treatment.

For patients with moderate to severe OUD who are reluctant to take medication, specific interventions can increase motivation to take and adhere to medications, including motivational interviewing, contingency management or peer support services.

In individuals who choose psychosocial treatment alone, we typically start psychosocial treatment with a multimodal program that includes weekly addiction counseling, participation in a mutual help group several times per week, and an evidence-based psychosocial treatment such as CBT, contingency management, or combined behavioral intervention. If appropriate, conversations about initiating MOUD can be woven into these psychosocial interventions. (See "Opioid use disorder: Psychosocial management" and "Substance use disorders: Psychosocial management".)

We consider overdose prevention training, for the patient, family, and household contacts and naloxone distribution to be particularly important interventions for individuals who refuse medication treatment as these individuals are at a higher risk of overdose than those who are treated with MOUD. (See "Prevention of lethal opioid overdose in the community".)

ASSESSMENT OF RESPONSE

We typically assess individuals treated with buprenorphine on a weekly basis, initially, as dose adjustments are often occurring. Individuals treated with methadone are seen and assessed daily in an opioid treatment program (also known as a methadone clinic). We ask about use of substances and frequency of use, negative consequences of use, and other related medical concerns (ie, infection, pain). Urine samples are regularly collected and tested for common substances used.

We adjust the frequency of monitoring and intensity of treatment based on the patient's clinical status and risk of return to use (eg, during periods of abstinence versus exacerbations).

We define an effective treatment response for opioid use disorder as sustained abstinence (at least six months) from illicit drug use and no heavy alcohol use, as confirmed by urine testing and/or reports from non-drug-using supports. However, other acceptable responses to treatment include remaining in treatment and continuing on medication, lower frequency of use, or diminished craving (with the understanding that the goal of treatment is cessation of use). Treatment failure may be indicated by ongoing illicit opioid use (eg, nearly every urine drug screen is positive for illicit opioids), poor attendance to treatment, diversion of medication, or nonadherence to medications.

While no specific time is generally accepted as indicating a patient has failed treatment, poor response after 6 to 12 months of treatment should result in a careful re-examination of the approach being used.

MANAGEMENT OF INADEQUATE RESPONSE

Our approach to individuals with suboptimal response is based on clinical experience. There are few clinical trials comparing different sequences of medications for opioid use disorder (OUD) following first-line treatment.

For all individuals — For all individuals with OUD who have an inadequate response or no response to first-line pharmacotherapy we typically offer psychosocial treatment (if the

individual is not currently receiving it). In individuals currently receiving psychosocial intervention, we increase the frequency of the intervention, or add a second psychotherapeutic intervention or both. As an example, in an individual who has not responded to the initial treatment (agonist or antagonist) and who is not in any form of psychosocial treatment, we offer addiction counseling, contingency management, mutual help groups, or other structured psychosocial intervention. If the individual is already in psychosocial treatment such as addiction counseling or mutual help groups, we either increase the frequency of the intervention or add a second intervention (ie, add cognitive-behavioral therapy to addiction counseling). Intensity of treatment can also be increased by use of more structured or controlled settings for patients with such needs (eg, residential care for patients without a house). (See "Opioid use disorder: Psychosocial management".)

For inadequate response to medication

Individuals on opioid agonist treatment

- For individuals who have an inadequate response to opioid agonist treatment, our initial step is to optimize the medication dose. For these individuals, an increase in the dose of the agonist treatment may be beneficial in reducing illicit use. (See "Opioid use disorder: Pharmacologic management", section on 'Buprenorphine: Opioid agonist' and "Opioid use disorder: Pharmacologic management", section on 'Methadone: Opioid agonist'.)

- For individuals initially receiving daily buprenorphine who do not have an adequate treatment response despite dose optimization, our next choice is either long-acting injectable (LAI) buprenorphine or methadone.

  We use shared decision-making while considering properties of each formulation and its administration that may be preferred for specific clinical scenarios. For example, methadone may be preferred in individuals with high levels of physical dependence due to greater opioid agonism. However, for individuals that have not reached their treatment goal due to adherence issues LAI buprenorphine may be preferred as it can be given monthly and, unlike methadone, does not require daily clinic visits. We also consider the individual's need for structured support. For example, for individuals who are socially isolated or lack outside support we often prefer to use methadone as the individual may benefit from the daily interaction and supportive therapy given in opioid treatment programs (ie, methadone maintenance programs in the United States provided more oversight and structure [39]). (See "Opioid use disorder: Pharmacologic management", section on 'Buprenorphine: Opioid agonist' and "Opioid use disorder: Pharmacologic management", section on 'Methadone: Opioid agonist'.)

- For individuals who fail to respond to optimal doses of either methadone or and LAI buprenorphine, we suggest a trial of the alternative opioid agonist (methadone or buprenorphine).

  - For those initially started on buprenorphine who have a poor response or unacceptable side effects, it is easy to switch immediately to methadone treatment.

  - For those initially started on methadone who have a poor response or unacceptable side effects, several days off of methadone is needed to avoid precipitated withdrawal when starting buprenorphine. The length of time depends on the dose of methadone.

  Alternatively, some uncontrolled case reports suggest that buprenorphine can be initiated at very low doses (also called microdosing) and gradually titrated up while continuing methadone [40]. When the buprenorphine dose reaches the typical therapeutic range, methadone can then be discontinued [41,42]. (See "Opioid use disorder: Pharmacologic management", section on 'Alternative induction methods for specific circumstances'.)

  Initial doses for opioid agonists are discussed elsewhere. (See "Opioid use disorder: Pharmacologic management", section on 'Buprenorphine: Opioid agonist' and "Opioid use disorder: Pharmacologic management", section on 'Methadone: Opioid agonist'.)

- For individuals who have tried methadone and both buprenorphine and LAI buprenorphine and can tolerate a week-long medically supervised withdrawal without becoming unstable, we suggest treatment with LAI naltrexone after medically supervised withdrawal. (See "Opioid use disorder: Pharmacologic management", section on 'Long-acting injectable naltrexone'.)

- For individuals who are in circumstances that lead to treatment interruption or discontinuation due to external circumstances (eg, the coronavirus disease 2019 [COVID-19] pandemic), extended take-home doses of opioid agonist medications appear to be associated with lower rates of treatment interruption and discontinuation in some subsets of individuals. (See 'Regulation in the United States' below.)

  For example, in an observational cohort study, among 21,297 individuals receiving opioid agonist treatment with either methadone or buprenorphine/naloxone some were permitted to begin take-home doses and/or receive extended take-home doses during the COVID-19 pandemic [43]. Initiation of take-home methadone was associated with lower risk of treatment discontinuation (hazard ratio 0.8, 95% CI 0.72-0.9), lower risk of treatment interruption (hazard ratio 0.8, 95% CI 0.67-0.95), and lower risk of opioid overdose (hazard ratio 0.73, 95% CI 0.56-0.96) than daily dispensed methadone. Increases

in pre-existing number of take-home doses were associated with lower risk of treatment discontinuation (hazard ratio 0.72, 95% CI 0.62-0.84) and lower risk of treatment interruption (hazard ratio 0.69, 95% CI 0.53-0.9) than weekly methadone dosing. In individuals receiving buprenorphine/naloxone, extended take-home doses were associated with decreased treatment interruption only in those that had been receiving weekly buprenorphine (hazard ratio 0.74, 95% CI 0.56-0.99). There were no other differences in outcomes between treatment groups in those receiving buprenorphine/naloxone.

The findings from the relaxation of take-home dosing of opioid agonist medications, as has been seen during the COVID-19 pandemic, has implications for whether to return to the treatment regulations and practices in place before COVID-19. However, greater access to opioid agonist medications needs to be balanced by awareness of the problems seen with wide availability of opioid pain medications in recent years, including increases in overdoses associated with widespread prescription of such medications.

Individuals on opioid antagonist treatment

- For individuals who have repeatedly returned to opioid use despite treatment with oral naltrexone, we typically offer a trial LAI naltrexone formulation if they have not already tried this medication.

- For individuals who have repeatedly returned to opioid use after trials with both oral and LAI naltrexone, we typically use buprenorphine as our next agent. However, if the treatment failure is thought to be secondary to high levels of physical dependence, our next choice is methadone. (See 'Pharmacologic management' above.)

Individuals in psychosocial treatment alone — For individuals who fail to stop using illicit opioids on a repeated basis after 30 days of psychosocial treatment alone, we favor encouraging the initiation of medication for OUD (MOUD).

We typically prefer motivational interviewing targeting MOUD engagement as a strategy to engage individuals who choose psychosocial treatment alone. Contingency management or peer support services can also be used to increase motivation to initiate medication.

If the individual continues to decline MOUD, we increase the intensity of the psychosocial treatment. Intensity may be increased by increasing the visit frequency, increasing the level of care, or adding another evidence-based psychosocial intervention such as contingency management. (See "Opioid use disorder: Psychosocial management".)

In individuals choosing psychosocial treatment alone, ongoing discussion about the benefits of medication should be part of the treatment, and the patient can be offered MOUD if treatment with psychosocial methods alone continues to be ineffective.

Assessment of the patient's goals can help guide psychosocial treatment and other services. For example, if the person's goal is substance use reduction, counseling can be directed towards this goal. If the person's goal does not include abstinence, but includes safer substance use or improved health and quality of life, treatment may involve psychoeducation around safer use strategies, connection to health and mental health treatment, or housing case management as needed.

Addressing nonadherence — For individuals with nonadherence to daily doses of buprenorphine or oral naltrexone, we suggest supervision from family members or other supports to increase adherence to the medication. If appropriate, contingency management can be used to improve medication adherence. (See "Substance use disorders: Training, implementation, and efficacy of treatment with contingency management" and "Opioid use disorder: Psychosocial management".)

If there are ongoing problems with adherence for these daily dose forms despite supervision, we suggest treatment with LAI naltrexone or a long-acting subcutaneous buprenorphine. (See "Opioid use disorder: Pharmacologic management".)

Clinical trials have found longer-acting formulations of buprenorphine [44-46] and naltrexone [5,33-35] to be more effective than placebo for opioid dependence in randomized trials. Additionally, longer-acting naltrexone (extended release [XR] or implant) has been shown to be more effective in treatment retention [37] or reducing return to use [47] than oral counterparts. For example, in a trial, 60 individuals with OUD were randomly assigned to oral naltrexone with behavioral therapy or XR-naltrexone with behavioral therapy [37]. At six months, individuals receiving XR-naltrexone had twice the rate of treatment retention compared with those taking oral naltrexone (57 versus 28 percent). Presently, the implant is available in only some parts of the world [48].

The efficacy, adverse effects, and administration of the long-acting medications are reviewed separately. (See "Opioid use disorder: Pharmacologic management", section on 'Long-acting injectable naltrexone'.)

INDIVIDUALS REFRACTORY TO ATTEMPTS WITH MULTIPLE DIFFERENT TREATMENTS

We continue to encourage engagement in treatment for individuals who are refractory to multiple different treatment types.

Patients may be refractory to treatment for several different reasons including nonadherence, high levels of physiologic dependence, psychosocial stressors, or poor coping skills. While we continue to address these issues both pharmacologically and with psychosocial interventions (eg, use of long-acting medications for nonadherence, use of methadone in those with high levels of dependence, contingency management) we offer case management and use other harm reduction efforts while attempting to retain individuals in treatment. Retention in treatment for opioid use disorder (OUD) is associated with reduced risk for all-cause mortality and overdose [14,49,50].

Case management and harm reduction efforts often include connection to syringe services programs or provision of safer drug use supplies, HIV and hepatitis C testing, housing, and care navigation (ie, helping patient connect to relevant social services like housing and mental health care). The availability of these services vary by location. Harm reduction efforts have been shown to reduce overdose deaths in communities where they have been implemented [51]. (See "Opioid use disorder: Psychosocial management".)

As with the initial selection of psychosocial interventions, efficacy trials comparing different approaches with combining or sequencing psychosocial interventions have not identified superior strategies.

Heroin maintenance programs are less commonly used worldwide. Several countries have studied or instituted programs that include provision of injectable heroin (diacetylmorphine) or hydromorphone to individuals with OUD who have failed other treatments [52-56]. In a review of randomized trials including over 2100 subjects with chronic opioid use disorder (ie, heroin), treatment with heroin-assisted treatment (diacetylmorphine) led to greater retention in treatment as compared with methadone maintenance treatment (odds ratio 2.1, 95% CI 1.7-2.5) [56]. Treatment of OUD with heroin maintenance programs is controversial and unavailable in most parts of the world [57].

DURATION OF THERAPY FOR RESPONDERS

For individuals who have responded to treatment of opioid use disorder (OUD), we prefer ongoing rather than episodic treatment.

The continuing care for addiction model emphasizes that substance use disorders are chronic and recurrent issues that warrant ongoing attention and management. We continue to monitor

individuals that have responded to treatment on at least a monthly basis for 6 months to 12 months and less frequently thereafter. For those individuals that have suboptimal response to treatment, we continue to monitor weekly or twice monthly. Continuing care is important for OUD, which is often chronic with a progressive trajectory. (See "Continuing care for addiction: Components and efficacy" and "Continuing care for addiction: Implementation".)

No controlled studies have evaluated the optimal length of time that individuals who have a good response to treatment for OUD should remain in treatment. Our practice in individuals with response to medication for OUD (MOUD) is as follows:

- **For individuals who want to remain on MOUD** – We support this strategy indefinitely. We also encourage adjunctive maintenance psychosocial treatment for all individuals who have responded to MOUD.

- **For individuals who want to discontinue agonist or antagonist treatment** – In individuals who are fully free of problematic substance use, are engaged in productive activities, and have stable interpersonal relationship for at least 6 to 12 months, we support discontinuation of MOUD at the patient's request. For those individuals on methadone or buprenorphine this should be done via slow taper; we suggest multimonth tapers (eg, over six months or more). Opioid agonist tapers that are longer and slower tend to have better outcomes [58,59], and should be individualized for the patient. Naltrexone can be discontinued abruptly. Length of treatment and tapering of medications in individuals who have responded to treatment are discussed elsewhere. (See "Opioid use disorder: Pharmacologic management".)

  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.

  In individuals who have been free of harmful substance use and have subsequently stopped agonist or antagonist treatment under medical supervision, we suggest ongoing monitoring and psychosocial treatment. If there is a return to use, or other new or worsening symptoms (eg, craving) we recommend resuming treatment. (See "Continuing care for addiction: Implementation" and "Continuing care for addiction: Components and efficacy".)

- **For the patient who responds to psychosocial treatment alone** – We typically continue psychosocial treatment indefinitely; an individualized treatment plan can be crafted for each patient with a general plan for continuing care. There are no data to guide the choice

of treatment length or intensity for these individuals. (See "Continuing care for addiction: Implementation".)

SPECIFIC PATIENT POPULATIONS

Individuals who have completed medically supervised withdrawal — In individuals who undergo medically supervised withdrawal our preferred treatment after completion of the withdrawal is with long-acting injectable naltrexone and psychosocial augmentation. However, we also consider prior response to treatment for opioid use disorder (OUD). For example, if the individual reports a prior response to methadone and poor response to naltrexone, we would use methadone.

Naltrexone provides assurance that a return to illicit opioid use will not result in the person experiencing a reinforcing effect from the opioid. In cases of treatment failure with naltrexone (ie, poor attendance or continual, ongoing opioid use, nearly every urine drug screen positive for illicit opioids), we transition to opioid agonist treatment with buprenorphine. In cases of high level of physical dependence, we often prefer methadone treatment. (See 'Management of inadequate response' above.)

> Medically supervised withdrawal can occur for a number of reasons including administrative discharge from a program, lack of access or financial means to pay for illicit opioids, and patient setting (individual is incarcerated). In some cases, medically supervised withdrawal may be patient preference (ie, when an opioid dependent individual wants a “break” from use of the drug). (See "Opioid withdrawal: Medically supervised withdrawal during treatment for opioid use disorder".)

The lowered physiological tolerance following medically supervised opioid withdrawal may increase some individuals’ risk of overdose and subsequent death if they return to using opioids to the same degree as prewithdrawal [9,60].

Pregnancy — The opioid agonists, methadone and buprenorphine, are effective pharmacotherapies for OUD in pregnancy and neither appears to be teratogenic [61].

Medically supervised opioid withdrawal and treatment with an opioid antagonist is not considered first-line treatment for pregnant women with OUD because of the lack of randomized clinical trials studying naltrexone in pregnancy and because of concerns about putting the expectant mother and fetus through the stress of an episode of withdrawal [62].

Treatment of OUD during pregnancy is discussed in detail elsewhere. (See "Opioid use disorder: Overview of treatment during pregnancy".)

Individuals hospitalized for medical illness

Already being treated for opioid use disorder — For individuals who are hospitalized for medical illness and who are taking opioid agonist or antagonist for treatment of OUD, we typically continue maintenance treatment at the current dose. We check with the opioid treatment program or prescriber to confirm the current dose and how recently it was given. In cases where the clinic is not available to verify the dose of medication, we often give methadone 30 mg to abort acute withdrawal signs and symptoms until further information is available. Buprenorphine is unlikely to cause respiratory depression and is typically continued at the dose reported by the patient until the actual dose can be verified.

We contact the outpatient treatment program or buprenorphine prescriber and arrange for continuation of treatment with the medication by that provider after discharge.

Untreated opioid use disorder — Hospitalization may provide an opportunity to start individuals with OUD on medication and engage them in care. Initiating MOUD during a hospitalization with linkage to outpatient treatment in patients with untreated OUD appears to be associated with reduced illicit opioid use, greater adherence to treatment, and decreased against medical advice discharge in comparison to those treated with medically supervised withdrawal from opioids and not started on MOUD [63-65]. Initiation of buprenorphine during hospitalization is summarized elsewhere. (See "Opioid use disorder: Pharmacologic management", section on 'Alternative induction methods for specific circumstances'.)

As examples:

- A clinical trial randomly assigned 139 patients to a five-day buprenorphine medically supervised withdrawal protocol versus buprenorphine induction with dose stabilization, and postdischarge transition to outpatient treatment [64]. At six-month follow-up, patients assigned to in-hospital buprenorphine initiation and outpatient linkage were more likely to be engaged in buprenorphine treatment and reported less illicit opioid use (incidence rate ratio 0.60, 95% CI 0.46-0.73) compared with patients assigned to medically supervised withdrawal alone.

- In a retrospective study, from among 2332 patients discharged from inpatient treatment for opioid use disorder, 21 percent (n = 493) started medication for opioid use disorder (MOUD; buprenorphine 77 percent, methadone 23 percent, naltrexone 0.5 percent) while the others were treated with medically supervised withdrawal and referral for follow-up

treatment [65]. Initiation of MOUD was associated with lower likelihood of discharge against medical advice (odds ratio 0.49, 95% CI 0.37-0.64), lower 30 day all-cause hospital readmission (odds ratio 0.61, 95% CI 0.47-0.8), and higher odds of post-discharge MOUD adherence (odds ratio 3.83, 95% CI 3.06-4.81).

Individuals at risk for or with prolonged QTc — For individuals with prolonged QTc (ie, ≥500 msec), we suggest using buprenorphine or naltrexone rather than methadone. Methadone use has been associated with QTc interval prolongation and torsade de pointes. This is most common when an individual overdoses while on a high treatment dose; however, it has been reported for individuals on therapeutic dose or with other risk factors. In some cases, this QTc prolongation has been fatal. However, for some individuals, the risk of OUD outweigh the risks of prolonged QTc interval with methadone [66-69].

Interactions between methadone and other drugs that can prolong QTc interval or that can slow methadone elimination are shown in the table (table 2 and table 3). (See "Acquired long QT syndrome: Definitions, pathophysiology, and causes".)

Individuals with pain — Acute pain in individuals with comorbid OUD may be particularly challenging to treat and may warrant more specialized treatment from a provider with experience in both disorders.

Details on management of acute pain in patients using medications for treating OUD are discussed in detail elsewhere. (See "Management of acute pain in adults with opioid use disorder", section on 'Patients on methadone maintenance therapy' and "Use of opioids in the management of chronic non-cancer pain", section on 'Chronic opioid therapy'.)

Individuals with psychiatric comorbidity — In individuals with comorbid opioid use and psychiatric disorder, our preference is to treat both disorders simultaneously. Coordinated care may be more effective than specialty care in different sites.

Psychiatric disorders and OUD have high rates of comorbidity [70]. Most commonly, bipolar and depressive disorders, anxiety disorders, posttraumatic stress disorder, personality disorders, sleep disturbance [71], and other substance use disorders are found in populations with OUD. This topic is discussed elsewhere. (See "Co-occurring schizophrenia and substance use disorder: Psychosocial interventions" and "Pharmacotherapy for co-occurring schizophrenia and substance use disorder" and "Treatment of co-occurring anxiety-related disorders and substance use disorders in adults".)

REGULATION IN THE UNITED STATES

Methadone and buprenorphine are regulated as controlled substances (schedule II and schedule III drugs, respectively) in the United States, with different requirements and settings for administering each drug.

To prescribe buprenorphine for patients with an opioid use disorder (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 OUD if permitted by applicable state law [72]. Methadone for the treatment of OUD may be administered only by licensed opioid treatment programs or licensed inpatient hospital units. There is also an emergency exception for short-term use to initiate methadone. Thus, the choice between the two medications can also be a choice between treatment environments and patient experiences. (See "Opioid use disorder: Pharmacologic management", section on 'Regulation of methadone in United States' and "Opioid use disorder: Pharmacologic management", section on 'Regulation of buprenorphine in United States'.)

COVID-19-related health care disruptions and the need for physical distancing led to measures to support continued access to opioid agonist therapy by many countries worldwide. This has led to increased take-home doses of opioid agonist treatment including for those previously deemed ineligible for this type of dispensing [73,74]. It appears that loosening of take-home medication restrictions in the United States has not been associated with increases in methadone-related opioid poisonings [75,76].

CLINICIAN EDUCATION AND TRAINING

The Substance Abuse and Mental Health Services Administration-funded Providers' Clinical Support System (PCSS) in the United States provides training and educational materials for clinicians prescribing medications for opioid use disorder (OUD). PCSS provides clinicians with access to a nationwide network of mentors for prescribing clinicians who are unfamiliar with the treatment of OUDs.

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".)

SUMMARY AND RECOMMENDATIONS

- **Before initiating treatment** – We use shared decision-making to establish a treatment plan. We consider the presence of physical dependence, prior treatment history, and patient preference. Additionally, we provide educational material about overdose protection and distribute naloxone. (See 'Before initiating treatment' above.)

- **Initial pharmacologic treatment** – An algorithm describes our approach to medication for opioid use disorder (MOUD) (algorithm 1).

  - For moderate to severe opioid use disorder (OUD; ie, individuals with physical dependence), we recommend first-line treatment with pharmacologic management, rather than psychosocial treatment alone (**Grade 1B**). (See 'Patients with physical dependence (moderate to severe disorder)' above.)

    For pharmacotherapy of moderate to severe OUD, we suggest buprenorphine rather than other medications (**Grade 2C**). Methadone is an effective alternative that may be more appropriate for those with higher levels of opioid dependence. We reserve naltrexone (long-acting) for those who decline or cannot tolerate buprenorphine or methadone or have completed medically supervised withdrawal.

  - For most patients with a mild OUD (ie, individuals without physical dependence), we suggest MOUD with psychosocial augmentation rather than either treatment alone. (**Grade 2C**). We suggest first-line treatment with long-acting injectable (LAI) naltrexone rather than other medications (**Grade 2C**). (See 'Patients without physical dependence (mild disorder)' above.)

- **Adjunctive psychosocial treatment** – For all individuals with OUD, we suggest adjunctive psychosocial treatment along with MOUD (**Grade 2C**). In individuals who prefer psychosocial treatment alone, we treat with a multimodal program that includes addiction counseling, mutual help groups, and a psychosocial treatment such as cognitive-behavioral therapy. (See 'Individuals who decline medication for opioid use disorder' above and 'Adjunctive psychosocial intervention' above.)

- **Assessment of response** – We assess response to treatment by the presence of illicit opioid use, medication adherence, treatment attendance, withdrawal and craving. Although sustained abstinence is the ultimate objective, other appropriate responses include adherence to treatment and reduced use. (See 'Assessment of response' above.)

- **For inadequate response** – Our approach is based on our clinical experience:
  - For inadequate response to optimized dosing of daily buprenorphine, our next choice is LAI buprenorphine or methadone. We individualize the selection depending on adherence, need for support, and level of dependence. (See 'Individuals on opioid agonist treatment' above.)
  - For inadequate response to either methadone or LAI buprenorphine at optimal dose, we prefer a trial of the other agonist. For inadequate response to all agonists we typically treat with medically supervised withdrawal followed by LAI naltrexone. (See 'Individuals on opioid agonist treatment' above.)
  - For inadequate response to oral naltrexone, we prefer LAI naltrexone. For inadequate response to both oral and LAI naltrexone we typically choose buprenorphine. However, if the inadequate response is due to high physical dependence we typically prefer methadone. (See 'Individuals on opioid antagonist treatment' above.)
  - For inadequate response to agonist, antagonists and psychosocial treatment, we favor increasing the intensity of psychosocial treatment. (See 'Individuals refractory to attempts with multiple different treatments' above.)
- **Duration** – We manage OUD as a chronic condition and continue MOUD and psychosocial treatment indefinitely. We strongly encourage that patients continue MOUD for a minimum of 6 to 12 months following stabilization prior to tapering off medications. (See 'Duration of therapy for responders' above.)

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