Opioid withdrawal: Medically supervised withdrawal during treatment for opioid use disorder

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INTRODUCTION

Medically supervised opioid withdrawal, also known as detoxification, involves the administration of medication to reduce the severity of withdrawal symptoms that occur when an opioid-dependent patient stops using opioids [1]. Symptoms of opioid withdrawal include drug craving, anxiety, restlessness, gastrointestinal distress, diaphoresis, and tachycardia. Medications used in the treatment of withdrawal symptoms include opioid agonists such as methadone and buprenorphine (a partial agonist), as well as alpha-2 adrenergic agonists such as clonidine and lofexidine.

The principal purpose of supervised withdrawal is to safely and successfully transition the patient to medication for opioid use disorder. Supervised withdrawal alone does not generally result in sustained abstinence from opioids [2], nor does it address reasons the patient became dependent on opioids or the damage that the addiction has done to relationships, employment, finances, and the mental, physical, and spiritual health of the patient. It is important to note that full detoxification from opioids is only achieved in transitioning a patient to the opioid antagonist intramuscular naltrexone; transitioning to either methadone or buprenorphine will still maintain the patient in a state of physiological dependence on opioid agonism.

This topic describes indications and contraindications, monitoring, treatment options, and selection among them in medically supervised opioid withdrawal. Clinical manifestations, course, assessment, and diagnosis of opioid withdrawal are described separately. The

management of unplanned withdrawal in the emergency department is also described separately, as is opioid withdrawal in adolescents. Pharmacotherapy and psychosocial interventions for opioid use disorder are also discussed separately. (See "Opioid withdrawal: Clinical features, assessment, and diagnosis" and "Opioid withdrawal in the emergency setting" and "Opioid withdrawal in adolescents" and "Opioid use disorder: Pharmacologic management" and "Opioid use disorder: Psychosocial management".)

INDICATIONS AND CONTRAINDICATIONS

Using medications to lessen the severity of withdrawal symptoms is indicated when opioid dependent patients abruptly stop taking the opioid. Patients may do so for a number of reasons, such as:

- As the first step in treatment for opioid use disorder, involving transition to an opioid or nonopioid treatment for opioid use disorder. (See "Opioid use disorder: Pharmacologic management".)
- To establish an abstinent state without withdrawal symptoms, which may be a requirement of the patient's setting or status (eg, incarceration, probation, or a drug-free residential program). (See "Opioid use disorder: Psychosocial management".)
- The patient ran out of the financial means to obtain opioids illicitly.
- The clinician who prescribed the opioid stopped doing so or transferred patient (eg, for breaking a treatment agreement).
- A patient dependent on heroin is hospitalized and lacked access to the drug.
- An opioid-dependent individual wants "a break" from use of the drug.
- A patient on maintenance methadone or buprenorphine has been administratively discharged from treatment.

Patients planning to stop an opioid analgesic that they have not misused or diverted are not typically referred for medically supervised withdrawal. These patients are more commonly tapered off the medication by the prescribing clinician over whatever period is needed to allow the patient to succeed with the taper (eg, weeks to months) [3]. Considerations in selecting these patients and approaches to the taper are described separately. (See "Use of opioids in the management of chronic non-cancer pain", section on 'Discontinuing therapy'.)

We agree with the recommendation of the American College of Obstetricians and Gynecologists that individuals who are pregnant with opioid use disorder start or continue treatment with an opioid agonist during pregnancy rather than undergo medically supervised withdrawal and attempt to maintain abstinence [4]. Despite earlier case reports, medically supervised withdrawal may be safely conducted during pregnancy [5]. Supervised withdrawal, however, presents a much higher risk to the mother and fetus due to the high rate of subsequent relapse (average 48 percent) [6]. Relapse to use of illicit opioids typically results in recurrent episodes of intoxication and withdrawal, with the potential for fetal growth delay, abruptio placentae, preterm labor, passage of meconium, and fetal death [4]. Lifestyle risks and poor prenatal care associated with ongoing illicit opioid use also contribute to worse maternal and fetal outcomes for women not in medication for opioid use disorder (MOUD) compared with those who remain on MOUD [7].

Females who refuse opioid-agonist treatment or do not have it available to them would need to undergo medically supervised withdrawal. This should be performed under the supervision of physicians experienced in prenatal care with fetal monitoring [8]. Withdrawal is safest in the second trimester and typically uses a slow methadone taper [9]. The use of buprenorphine or methadone during pregnancy is discussed separately. (See "Opioid use disorder: Overview of treatment during pregnancy" and "Opioid use disorder: Pharmacotherapy with methadone and buprenorphine during pregnancy".)

MONITORING

For the purposes of short-term medically supervised withdrawal, it is best to use clinical observation and a structured instrument with a standardized scoring system to assess the progress and severity of withdrawal and to guide medication administration. The severity of withdrawal and its exact symptoms do not always correlate with the daily morphine equivalent dose of the previous drug or the reported duration of use [10], and significant individual differences in withdrawal symptoms can occur [11].

We use the Clinical Opioid Withdrawal Scale (COWS) (calculator 1) (table 1) [12] because of its ease of use and sensitivity. The COWS rates the severity of 11 signs/symptoms of opioid withdrawal on a scale from 0 to 5. The COWS has been well validated and shows interrater correlation coefficients as high as 0.975 [13,14]. We administer the COWS multiple times each day during supervised withdrawal. In the sections on Administration of standard medications, below, we describe specific measurement intervals and threshold COWS scores used to guide dosing decisions. (See 'Buprenorphine-naloxone' below and 'Methadone' below and 'Alpha-2 adrenergic agonists' below.)

Other well-described instruments are listed below; it is most important that staff become familiar with one tool and use it consistently to achieve high interrater reliability:

- Objective Opioid Withdrawal Scale (OOWS) [15]: 13 signs of opioid withdrawal scored present or absent
- Subjective Opioid Withdrawal Scale (SOWS) [15]: 16 subjective symptoms self-rated 0 to 5
- Clinical Institute Narcotic Assessment (CINA) [16]: 11 self-report and observer rated items, scored 0 to 4 or 0 to 5

Serial monitoring can also reveal unanticipated trends. As an example, if symptom severity does not decrease over time in response to a standard medication (ie, failure to respond to treatment), review recent use history with the patient and obtain urine toxicology to rule out unreported use of another substance that may be affecting the course of the supervised withdrawal.

MEDICATION STRATEGIES

In this section, we describe our approach to medically supervised opioid withdrawal. We then go into greater detail about each medication strategy. Medications are described in four categories:

- Standard protocols with primary medications that target a broad range of withdrawal symptoms (see 'Standard treatments' below)
- Adjunctive medications used in conjunction with standard treatments targeting specific symptoms (see 'Adjunctive medications' below)
- Accelerated withdrawal protocols using primary medication combinations and adjunctive drugs (see 'Naltrexone-accelerated withdrawal' below)
- Alternative treatments, mostly medications, for which available research is insufficient to establish their efficacy in supervised withdrawal (see 'Other' below)

Many of these medications, described below, have been tested in randomized trials against placebo. Some have also been subjected to head-to-head trials; however, our ability to draw definitive conclusions from comparative trials has been limited by variability among treatment protocols.

Approach to treatment — For most patients with physiologic dependence on opioids undergoing medically supervised withdrawal, we suggest first-line treatment with buprenorphine rather than methadone or an alpha-2 adrenergic agonist.

Buprenorphine versus methadone — Buprenorphine and methadone have comparable efficacy in supervised withdrawal [17,18]. A meta-analysis of five clinical trials with 457 patients found that a similar proportion treated with buprenorphine completed supervised withdrawal compared with patients treated with methadone (53 versus 55 percent; risk ratio 1.04 [0.91, 1.20 95% CI]) [18]. Considerations favoring buprenorphine as our first-line medication include (see 'Buprenorphine-naloxone' below and 'Methadone' below):

- Methadone's risk of lethal overdose practically limits its use to monitored inpatient settings, while buprenorphine provides greater flexibility in treatment setting.
- In our clinical experience, when administered for detoxification and not maintenance, buprenorphine is more effective at suppressing and controlling withdrawal symptoms as the taper nears completion compared with methadone, with which symptoms are more likely to persist or increase again following taper.

Opioid agonists versus alpha-2 adrenergic agonists — Buprenorphine and methadone have been found to be superior to clonidine or lofexidine in supervised withdrawal [17,18]:

- A meta-analysis of 1264 supervised withdrawal participants found that those treated with buprenorphine were more likely to complete treatment compared with those receiving alpha-2 adrenergic agonists (risk ratio 1.59 [1.23, 2.06 95% CI]) [18]. There was no difference in the incidence of adverse effects between groups. (See 'Buprenorphine-naloxone' below and 'Alpha-2 adrenergic agonists' below.)

  As an example, a clinical trial of 344 opioid-dependent patients found that a greater proportion of buprenorphine-treated patients completed supervised withdrawal with a last day urine drug screen free of illicit opioids compared with patients receiving clonidine (46 versus 11 percent) [19].

- A meta-analysis of five clinical trials with 340 patients found the alpha-2 agonists to be somewhat less effective than methadone taper in ameliorating withdrawal symptoms, as measured by the likelihood of severe withdrawal (risk ratio 1.18, 95% CI 0.81-1.73) [20]. (See 'Methadone' below and 'Alpha-2 adrenergic agonists' below.)

In programs and settings that prohibit use of controlled substances including opioid agonists (eg, drug-free residential programs and prisons), we suggest use of an alpha-2 adrenergic

medication for supervised withdrawal. No significant difference in efficacy has been found between clonidine and lofexidine; lofexidine may be better tolerated and has been approved by the US Food and Drug Administration (FDA) for treatment of acute opioid withdrawal [21].

These and other medications for supervised opioid withdrawal are described in greater detail below.

Standard treatments

Buprenorphine-naloxone — Buprenorphine, a partial mu-opioid agonist and kappa opioid antagonist, is an effective treatment for opioid withdrawal symptoms. Advantages to its use in supervised withdrawal include a long duration of action, higher affinity for mu-opioid receptor than all other opioids, slow dissociation from the receptor, and greater safety in overdose than full agonists such as methadone [18,22].

Buprenorphine is administered in a combination preparation with naloxone, an opioid antagonist that has poor sublingual bioavailability [23]. The inclusion of naloxone discourages intravenous buprenorphine misuse since the naloxone can precipitate withdrawal when administered parenterally to patients with physiologic dependence on full agonist opioids. The ratio of buprenorphine to naloxone is 4:1. More detailed information on buprenorphine's pharmacology and use in maintenance treatment are discussed separately. (See "Opioid use disorder: Pharmacologic management", section on 'Buprenorphine: Opioid agonist'.)

A relative disadvantage of buprenorphine is that it can precipitate or worsen opioid withdrawal symptoms in those physiologically dependent on opioids if not administered carefully. To avoid this, the patient must be in a state of mild to moderate withdrawal **before** taking their first dose of buprenorphine (for example, having a Clinical Opioid Withdrawal Scale [COWS] score greater than 10 to 12). When buprenorphine is administered to a patient in withdrawal, they experience a net gain in opioid agonism and relief from withdrawal symptoms. Low-dose induction has been described as a way to introduce buprenorphine while continuing agonist exposure (a known prescribed medication). This method has been used for those to be indicted onto buprenorphine maintenance, rather than for supervised withdrawal (see "Opioid use disorder: Pharmacologic management", section on 'Alternative induction methods for specific circumstances'). In contrast, single high-dose buprenorphine (32 or 64 or 96 mg), done on an inpatient basis, was used in those in moderate opioid withdrawal, resulting in reduced craving over a five-day period, though other opioid withdrawal symptoms were not described [24]. Since 2023 in the United States, buprenorphine can be prescribed by all with a controlled substance license. (See "Opioid use disorder: Pharmacologic management", section on 'Regulation of buprenorphine in United States'.)

Buprenorphine potentially can cause respiratory depression, but its partial agonist properties limit this effect by preventing complete activation of mu-opioid receptors, making the drug relatively safe in overdose. Buprenorphine has been reported to cause fatal respiratory depression when taken in combination with other substances, especially benzodiazepines and alcohol [25], or when administered intravenously at high doses [26]. (See "Opioid use disorder: Treatment overview" and "Opioid use disorder: Pharmacologic management", section on 'Adverse effects'.)

Common side effects of buprenorphine, which are discussed in more detail separately, include sedation, headache, nausea, constipation, and insomnia. (See "Opioid use disorder: Pharmacologic management", section on 'Adverse effects'.)

Efficacy — Because methadone was a well-established, effective medication for medically supervised opioid withdrawal when buprenorphine was being tested, there are no placebo-controlled trials of buprenorphine's efficacy in medically supervised withdrawal. Comparative clinical trials, described above, have found that buprenorphine has efficacy in supervised withdrawal that it as good as or somewhat better than methadone, and superior to alpha-2 adrenergic agonists. (See 'Buprenorphine versus methadone' above and 'Opioid agonists versus alpha-2 adrenergic agonists' above.)

Administration — Buprenorphine administration to alleviate opioid withdrawal symptoms and subsequent taper can often be accomplished on an outpatient basis. Level of care considerations for medically supervised withdrawal are discussed in detail separately. (See "Opioid withdrawal: Clinical features, assessment, and diagnosis", section on 'Level of care determination'.)

Induction with buprenorphine is frequently conducted with direct observation by the prescriber. As familiarity with this agent has been gained, some providers will utilize "home induction," where buprenorphine is prescribed and then taken at home as directed. In observed induction, response to a first dose is assessed before allowing the patient to return home. The patient typically goes home with a second dose to be taken if needed six hours or more later and returns the next day. For home induction, the patient is advised to stop using their misused opioid until mild to moderate opioid withdrawal symptoms occur, after which the patient can take their first dose. Again, a second dose should be available if withdrawal symptoms are not controlled or return.

As described below, a typical induction (initiating the medication), stabilization (bringing withdrawal symptoms under control), and taper typically has a duration of 5 to 10 days, though longer tapers (up to 28 days) appear to improve symptom control. The optimal taper has not

been established [27]. A four-week taper has not consistently shown improved treatment retention or relapse rates [28,29], though one well-controlled trial with high intensity treatment including induction onto naltrexone and daily visits for 28 days, and then thrice weekly visits for the following eight weeks, did show better abstinence rates for the four-week taper versus one- or two-week tapers at the end of 12 weeks of treatment [30].

- **Induction (day 1)** – The timing of buprenorphine initiation is based in part on the half-life of the prior opioid and the time of last use. A patient dependent on a short-acting agent such as oxycodone would be advised to take their last dose 6 to 12 hours before coming in for initiation. A patient who has been regularly using methadone, a long-acting drug, would take their last dose 36 hours before treatment. For patients transitioning to supervised withdrawal from methadone maintenance treatment, patient's daily dose should gradually be tapered to 30 mg/day before buprenorphine initiation [31]. Alternatively, a patient on a higher dose of methadone can be transitioned to 12 mg per day buprenorphine over three to seven days using a low-dose induction strategy, and then buprenorphine tapered as described below [32]. Timing can be informed by patients, who usually know how long after their withdrawal symptoms will start after last use.

  Once the patient is in withdrawal, as assessed by objective scoring of signs of withdrawal (COWS 12 or greater), they are given the first dose of buprenorphine, 2 to 4 mg sublingually. In most cases, 4 mg is well tolerated and allows for fewer reassessments later. Relief of symptoms can occur in minutes, though often 30 to 60 minutes is needed for the full effect. Many will report reductions in COWS score to 5 or less.

  If the patient experiences sufficient relief after the initial 4 mg dose (COWS score less than 6), vital signs are stable, and there are no other adverse effects, the patient can go home with a second 4 mg buprenorphine dose, which they are instructed to take if withdrawal symptoms and/or craving becomes prominent prior to the next morning. For inpatients, a COWS score that initially improves and then increases to 10 or more can trigger the second 4 mg dosing in two hours or more.

  If withdrawal symptoms are insufficiently controlled following the first dose, up to 4 mg can be given within an hour, which almost always provides marked relief, after which the patient may go home. Given they will not have another dose of buprenorphine-naloxone to use, the patient might be provided scripts for an alpha-2 adrenergic agonist (eg, clonidine), as well as adjunctive, symptomatic medications, based on the most prominent symptoms of withdrawal they report. Some providers allow a first day dose up to 12 mg of buprenorphine. (See 'Alpha-2 adrenergic agonists' below and 'Adjunctive medications' below.)

If withdrawal symptoms worsen following the first dose, it is best to provide a second 4 mg buprenorphine dose along with clonidine plus adjunctive, symptom specific medications, as described below.

A first-day total buprenorphine dose greater than 8 mg may be an indicator that the patient would be better served in an inpatient setting. (See "Opioid withdrawal: Clinical features, assessment, and diagnosis", section on 'Level of care determination'.)

- **Stabilization** – The goal of stabilization is to reduce withdrawal symptoms to a minimal level on a stable daily medication dose. Day 2 dosing is based on the total amount of buprenorphine taken on day 1 and the presence/absence of continued withdrawal symptoms. If the patient takes a total of 8 mg on day 1 (usually the case) and reports minimal-to-no withdrawal symptoms upon returning for day 2, 8 mg can be given as a single dose.

  If the subject reports continued withdrawal symptoms and/or craving on day 2, the daily dose can be raised to 12 mg/day. Provided other new issues have not arisen, the patient can return to their outpatient or inpatient setting.

If the patient continues to report ongoing symptoms upon returning for day 3, the dose can be raised to 16 mg/day. In most cases (other than withdrawal from long-acting opioids), poor symptom or marked craving on day 3 bodes badly for a successful withdrawal off opioids. Reassessment should be made as to whether the patient might be better served by transitioning to continuing office-based opioid treatment with buprenorphine or referral to an outpatient treatment program (OTP) for methadone maintenance [27]. (See "Opioid use disorder: Pharmacologic management".)

- **Taper** – Once withdrawal symptoms have been well controlled for 24 hours, a gradual taper of patient's daily buprenorphine dose is started. Buprenorphine's relatively long duration of action allows for faster tapering, such as:

  - From 12 mg – Decreases of 2 mg/day over each of the next five days (ie, 10 mg to 8 mg to 6 mg to 4 mg to 2 mg/day).

  - From 16 mg – Decreases of 4 mg for two days then decreases of 2 mg/day for three days (ie, 12 mg to 8 mg to 6 mg to 4 mg to 2 mg/day).

  Decreases from the higher doses seem to be experienced with fewer symptoms than decreases from 4 mg and below. If the patient experiences continued withdrawal

symptoms or symptoms emerge as lower doses are reached, there are several therapeutic options:

- Slow the taper and hold at the lowest effective dose
- Provide clonidine and adjunctive medications, as described below to allow the taper to proceed (see 'Alpha-2 adrenergic agonists' below and 'Adjunctive medications' below)
- Raise the buprenorphine dose and provide as continuing office-based opioid treatment, with taper attempted at a later date (see "Opioid use disorder: Pharmacologic management")
- Modify the patient's environment to reduce cue or stress-induced relapse risk (eg, residential treatment)

Methadone — Methadone, a full mu-opioid agonist, is an effective treatment for opioid withdrawal symptoms. In contrast to buprenorphine, methadone does not induce withdrawal symptoms when given to a patient with opioid agonist in their system. Methadone has an additive effect to opioids that are already present.

Disadvantages of methadone include that it is not safe in overdose. United States regulations preclude providing the medication to take home except when used for pain management. For these reasons, its use in supervised withdrawal usually requires residential or inpatient treatment. Supervised withdrawal with methadone in the United States is legally restricted to a federally designated OTP, to a maximum of three days in other outpatient settings as the patient awaits admission to an OTP, or to an inpatient hospital setting. When used in a residential or inpatient setting, the admission must be for a reason other than opioid use disorder alone, in which case the methadone taper must be conducted within an OTP.

Adverse effects of methadone include prolonged QTc and the potentially fatal cardiac arrhythmia [33,34]. Methadone should **not** be used if the QTc is over 500 msec and used with caution if between 450 to 500 msec. Caution should also be used in patients with an elevated risk of bradycardia, hypokalemia, hypomagnesemia, or hypocalcemia, as these will raise risk of Torsades de Pointes, and with concurrent use of psychotropics or other medications that prolong the QTc interval.

Overdose with methadone can be lethal, due to arrhythmia or respiratory depression. Overdose is treated with intranasal naloxone (4 or 8 mg) or intramuscular naloxone (0.4 or 0.8 mg) [35], with repeated doses as needed and rapid transfer to a medical unit [34]. Risks associated with methadone overdose are described in more detail below.

Because of methadone's long half-life, its dose needs to be increased cautiously on day 1 of medically supervised withdrawal. The drug will accumulate faster than it is eliminated over a 24 hour dosing interval and can reach dangerous levels. The first dose should not exceed 30 mg, and no more than 40 mg given on the first day [27].

Acute side effects of methadone include constipation, sedation, excess sweating, peripheral edema, and erectile dysfunction. Constipation should be aggressively treated with docusate/sennosides. Other side effects should abate with the taper. Significant oversedation should not be expected and would indicate too high a dose has been used. Adverse/side effects, drug interactions, and cardiac contraindications/monitoring are described in more detail separately. (See 'Indications and contraindications' above and "Opioid use disorder: Pharmacologic management", section on 'Methadone: Opioid agonist' and "Prevention of lethal opioid overdose in the community".)

Efficacy — A meta-analysis of two randomized trials found methadone to be superior to placebo in medically supervised opioid withdrawal [36]. The trials with a total of 38 patients found that patients receiving methadone were more likely to complete treatment (94.7 versus 47.3 percent) and experienced less severe withdrawal symptoms.

Administration — Methadone taper is based on the substitution of a long-acting opioid for the shorter-acting opioid (eg, heroin), bringing withdrawal symptoms under control, and then slowly tapering the methadone. There are many different approaches to the dosing of methadone substitution and taper. Here we describe our approach as well as some variations.

The duration of methadone taper ranges from five days for an inpatient to 14 days or longer for an outpatient. OTPs might utilize a treatment plan involving a slower taper of 30 to 180 days (long-term detoxification). A briefer, simple paradigm is a five-day course of 25 to 20 to 15 to 10 to 5 mg over five days. We prefer a symptom-guided approach to dosing, described below:

- **Induction (day 1)** – In the absence of opioid withdrawal symptoms/signs, it is difficult to gauge the efficacy of an initial methadone dose; thus, the first dose of methadone is not started until the patient enters mild to moderate withdrawal (a score of 10 to 12 on the COWS (table 1)).

  Dosing of methadone on day 1 should not rely as much on the reported opioid agent and daily dose as it should seek a balance between controlling withdrawal symptoms and avoiding oversedation and motor impairment. Conversion of morphine equivalents to methadone dose is difficult as the values vary based on methadone dose and previous tolerance.

The initial methadone dose on day 1 can vary from 10 to a maximum of 20 mg, and the dose over the first 24 hours must not exceed 40 mg. Considerations in choosing an initial methadone dose include:

- A typical initial methadone dose is 20 mg.
- One could start with 10 mg in a patient who presents with a history of low daily opioid use, such as one to two bags of heroin per day or 5 to 10 mg oxycodone per day.
- A more incremental approach requiring closer monitoring is to start with a 10 mg dose irrespective of opioid use history and reassess COWS after two hours. If COWS is:
  - Less than 6, observe
  - 6 to 12 give a 5 mg dose
  - 12 or over, give a 10 mg dose

  After a second dose, reassess COWS after another two hours, and repeat.

- **Stabilization** – On the morning of day 2, if COWS is under 6, the total dose used over the first 24 hours should be provided on day 2. A daily dose of 40 mg or less will control symptoms in most patients. If COWS remains between 6 to 12 on day 2, the total day 2 dose might be raised by 20 percent (up to 40 mg). If after two hours this does not bring COWS below 6, additional adjunctive treatment as described below may be needed. (See 'Adjunctive medications' below.)

  If COWS on day 2 is over 12, or there are other indications that withdrawal symptoms cannot be controlled, a period of maintenance treatment can be considered.

- **Taper** – Dose taper can typically be started after day 2. Dose reduction can be as rapid as 20 percent per day on an inpatient unit, but tapers of one to two weeks or longer are the norm. As an example, one might begin with 40 mg methadone day 1 and then decrease by 10 mg/day until 10 mg is reached, then by 2 mg per day [37]. Other tapering strategies have been described [37,38]. Once 10 to 15 mg a day is reached, patients typically experience greater withdrawal symptoms with further dose reductions, necessitating addition of clonidine and adjunctive medications (table 2) or slowing of the taper [39]. (See 'Alpha-2 adrenergic agonists' below and 'Adjunctive medications' below.)

  The specific approach to tapering appears to be less important to a successful supervised withdrawal than the patient's internal motivation and the adequacy of the overall treatment plan [40].

Supervised withdrawal using methadone is not over with the last daily dose. Due to the drug's long half-life, increased withdrawal symptoms and/or craving can emerge two or more days after the last dose [41,42]. Clonidine and adjunctive medications (table 2) can provide relief [39]. Patients are highly vulnerable to relapse following completion of withdrawal, underscoring the importance of psychoeducation on the risk of overdose with recurrence of use, provision of naloxone rescue agents, and the transition to maintenance treatment if clinically appropriate. (See 'Alpha-2 adrenergic agonists' below and 'Adjunctive medications' below.)

Alpha-2 adrenergic agonists — Alpha-2 adrenergic agonists, including clonidine and lofexidine, lessen many symptoms of opioid withdrawal [43]; they most effectively relieve the autonomic symptoms of sweating, diarrhea, intestinal cramps, nausea, anxiety, and irritability [39,44]. They are least effective for myalgias, restlessness, insomnia, and craving. Compared with reducing doses of methadone, these agents have been found to be comparably efficacious but more likely to cause side effects [20]. Patients typically prefer opioid agonists over alpha-2 adrenergic agonists.

In many clinical settings, alpha-2 adrenergic agonists are no longer used as a primary medication in supervised opioid withdrawal; instead, they are mostly used as adjuncts to treatment with buprenorphine or methadone [45]. They are used first-line in supervised withdrawal in prisons and other environments that prohibit the use of opioid agonists and other controlled substances. Diversion and misuse of adrenergic agonists has been reported (for their sedating effect and for self-treatment of withdrawal symptoms), but the risks are relatively low [46]. (See 'Adjunctive medications' below.)

Alpha-2 adrenergic agonists act on presynaptic receptors that autoregulate noradrenaline release. Hyperactivity of the noradrenergic cell bodies of the locus coeruleus driven by an up-regulated cyclic adenosine monophosphate system leads to a well-defined opioid withdrawal syndrome in animal models [47]. Alpha-2 adrenergic agonists reduce withdrawal symptoms by decreasing locus coeruleus hyperactivity [43]. Drugs of this class have anxiolytic properties by lowering circulating noradrenaline [48].

Among the centrally acting alpha-2 adrenergic agonists that are available in the United States, clonidine is the most widely used for opioid withdrawal [49], while lofexidine was approved for use in 2018 [50]. Tizanidine has not been widely studied as a primary detoxification agent; rather, it is used to relieve muscle spasms occurring during opioid withdrawal. (See 'Adjunctive medications' below.)

Contraindications to the use of this class of agent include hypotension, moderate or worse renal insufficiency, cardiac instability, pregnancy, and psychosis. Caution should be used when coadministered with sedating medications such as tricyclic antidepressants and antipsychotics. Side effects, principally hypotension and sedation, limit the use of these drugs. Though lofexidine induces less hypotension than clonidine, it is reported in rare cases to prolong QTc [21,51,52].

Efficacy — There is strong support from clinical trials for the efficacy of alpha-2 adrenergic agonists in withdrawal symptom control and treatment completion compared with placebo [17,51]. A meta-analysis of three clinical trials [51] with a total of 148 opioid dependent patients found that these medications were superior to placebo for treatment completion (55 versus 29 percent; risk ratio 1.95 [1.34, 2.84 95% CI]). As an example [53], a clinical trial in 68 opioid-dependent inpatients found that patient treated with lofexidine, compared with placebo-treated patients, were more likely to complete treatment (34 versus 15 percent) and less likely to experience severe withdrawal symptoms (14 versus 30 percent). A 2017 FDA registration trial for the United States demonstrated the superiority of lofexidine compared with placebo on protocol completion (53 versus 35 percent) [54]. Tizanidine was examined in one study for use in opioid withdrawal [55]. Two small studies, yet to be replicated suggest baclofen, a GABA-B agonist, may be superior to clonidine in speed of suppression of opioid withdrawal symptoms, as well as resulting in lower Subjective Opioid Withdrawal Scale (SOWS) scores at days 7 and 14 of supervised opioid withdrawal treatment [56,57].

A meta-analysis of multiple randomized trials found alpha-2 adrenergic agonists to be comparable to reducing doses of methadone in ameliorating opioid withdrawal symptoms in patients with opioid use disorder [20]. No differences were seen between the treatments in severe withdrawal symptoms (risk ratio 1.18, 95% CI 0.81-1.73), peak withdrawal score, overall withdrawal severity, and rate of treatment completion. The duration of treatment was longer with reducing doses of methadone. Hypotensive and other adverse effects were more likely with alpha-2 adrenergic agonists.

Direct comparison of lofexidine and clonidine has not been definitive, but available research suggests equal efficacy between the two drugs with a trend towards less hypotension with lofexidine [58].

Administration — Clonidine can be taken orally or administered via a clonidine patch, changed weekly, at doses equivalent to oral clonidine 0.1, 0.2, and 0.3 mg twice daily. Many programs do not use clonidine patches for supervised withdrawal because of the potential need to make frequent dose adjustments, while other programs prefer clonidine patches because they minimize interruptions and do not require patient requests for medication, which can be

difficult to distinguish from drug seeking. The transdermal patch does not provide adequate blood levels for the first 72 hours after application, so oral dosing is required for the first three days regardless of whether the patch is used.

Relief from withdrawal symptoms typically occurs within 30 minutes after a dose. The dose and frequency of clonidine administration are typically limited by sedation and/or orthostatic hypotension; dry mouth and constipation are also common.

- **Day 1** – To initiate withdrawal with clonidine, opioids are abruptly stopped. Sitting and standing blood pressure are checked prior to treatment and clonidine is given if the blood pressure is at or above 90/60, heart rate greater than 60, and orthostatic hypotension is not present. A test dose of clonidine 0.1 mg (0.2 mg if patient weighs 90 kg [approximately 200 pounds] or more) is given. After 45 minutes, if the blood pressure and pulse remain within these parameters, and symptoms remain prominent (COWS score greater than 8), additional 0.1 mg doses can be administered and repeated every 45 to 60 minutes up to four doses. Subsequently, up to 0.3 mg of clonidine can be given every six hours, with dosing determined by response:

  - For a COWS 8 to 12, give 0.1 mg
  - For a COWS over 12, give 0.2 mg
  - For a COWS exceeding 24, consider changing strategy to buprenorphine-naloxone or methadone

  For patients over 90 kg (approximately 200 pounds), the doses of clonidine can be raised by 0.1 mg. The total daily dose typically does not exceed 0.8 mg/day (or for patients 90 kg [approximately 200 pounds] or more, 1.2 mg/day).

- **Day 2 and after** – The amount of clonidine provided on day 1 is totaled and provided daily in divided doses three or four times per day on day 2 typically through day 4. Tapering is usually started around day 5 based on the patient's level of comfort (ie, minimal symptoms). Tapering is done gradually, with the dose reduced by 0.1 to 0.2 mg/day, to prevent rebound hypertension, especially with recent or current use of beta-blockers.

If supervised withdrawal is conducted on an outpatient basis, the vital signs after the first dose should be assessed as above. If the medication is tolerated, no more than a two-day supply should be given before vitals are again assessed. The taper of clonidine is usually completed in 6 to 12 days, though some patients remain on the agent during maintenance naltrexone treatment.

A typical total daily dose of lofexidine is 0.54 mg/day administered in three divided doses. Lofexidine requires less concern for hypotensive effects; again, taper over two to four days to reduce hypertensive rebound.

When alpha-2 adrenergic agonists are used to treat residual withdrawal symptoms as an adjunct to supervised withdrawal with buprenorphine or methadone taper, the COWS or other scoring instrument can be used to gauge whether an additional dose of the taper agent is needed or whether dosing of clonidine, as described for day 1 above, might be added.

Adjunctive medications — Patients with physiologic dependence on opioids undergoing supervised withdrawal with an opioid agonist, opioid partial agonist, or alpha-2 adrenergic agonist often experience some withdrawal symptoms during the treatment and taper periods. Symptom-specific, adjunctive medications (also known as symptomatic treatment) are used to provide targeted relief of the symptoms below:

- Abdominal cramping
- Diarrhea
- Nausea
- Insomnia
- Muscle aches
- Anxiety/restlessness

Adjunctive medications used to treat these symptoms are described in a table (table 2). In addition, alpha-2 adrenergic agonists (described above as a primary medication) can also be used as an adjunct to supervised withdrawal with an opioid agonist. (See 'Alpha-2 adrenergic agonists' above.)

Several medications are available for each category of target symptoms (table 2). Clinical staff typically come to prefer one or two medications in each category with which they have become familiar. We note our first-line preferences at the top of each category, but clinical circumstances can favor other options.

Although adjunctive medications are typically needed more frequently in conjunction with alpha-2 adrenergic agonists, they are useful in conjunction with opioid agonists and partial agonists as well. In a study of 234 patients treated with buprenorphine for opioid withdrawal, even among patients receiving 16 mg/day of buprenorphine, a majority of patients needed at least one adjunctive medicine for relief of anxiety, restlessness, or arthralgias [19].

Benzodiazepines are sometimes used to treat anxiety, restlessness, and muscle spasm during inpatient supervised withdrawal; however, their use is to be avoided if possible. Prescribed

benzodiazepines can confound urine drug screen surveillance for illicit benzodiazepine use, they are addictive, and they increase the chance of respiratory suppression when coadministered with methadone and buprenorphine. Their use should be reserved for inpatient settings, where frequent clinical monitoring can be performed.

Comorbid psychiatric disorders and medications may impact the choice of symptomatic treatments during the withdrawal. Anxiety disorders, including panic disorder, must be recognized and adequately addressed to facilitate completion of supervised withdrawal. The risk of suicide is elevated in anxiety and mood disorders and must be constantly assessed during the course of detoxification. Trauma-based conditions, such as posttraumatic stress disorder, may adversely affect the patient's ability to tolerate residential or inpatient environments. Lithium levels can vary markedly with withdrawal-associated dehydration and must be monitored closely; lithium can prolong QTc [59]. Carbamazepine may increase methadone dosing needs, and psychotropics strongly interacting with the CYP2D6 and 3A4 systems may affect levels of methadone and, to a lesser extent, buprenorphine. (See "Opioid withdrawal: Clinical features, assessment, and diagnosis", section on 'Co-occurring conditions'.)

Naltrexone-accelerated withdrawal — Protocols to accelerate medically supervised withdrawal aim to reduce the transition time to naltrexone treatment of opioid use disorder, thereby reducing risk of relapse, treatment drop-out, patient inconvenience, length of inpatient or residential stay, and treatment costs [60,61]. Naltrexone-accelerated withdrawal was initially developed with the goal of shortening the withdrawal period and not necessarily with the goal of transitioning a patient onto naltrexone maintenance [62]. These approaches are labor intensive and result in greater discomfort early in the course of withdrawal. As such, they require above average clinical skill in monitoring and management of withdrawal symptoms, and they are not used outside of clinical settings specialized in opioid withdrawal treatment and even then, used infrequently.

A resurgence in interest in development of naltrexone-accelerated withdrawal protocols has arisen with the approval of long-acting injectable naltrexone (LAI-NTX) for the treatment of opioid use disorder. The chief advantage of this agent is the reduced opioid-free period of 7 to 10 days between cessation of opioid use and initiation of the opioid antagonist [63,64].

A well-described protocol for naltrexone-accelerated withdrawal follows [65]:

- Patients abstain from opioids 12 to 24 hours before arriving day 2 in clinic.
- On day 2, as long as COWS >5, buprenorphine-naloxone 2 mg, then every one to two hours, to a maximum of 8 mg buprenorphine-naloxone on day 2.

- On days 3 to 8, standing clonidine 0.1 to 0.2 mg every four hours and clonazepam 0.5 mg four times daily are used.

- On day 4, 10 mg prochlorperazine is given orally (PO) as a pretreatment, then 1 mg oral naltrexone (only available from a compounding pharmacy, which may be impractical for routine clinical use).

- On days 5 to 7, 3, 12, and 25 mg oral naltrexone (only available from a compounding pharmacy) are given, then on day 8 LAI-NTX 380 mg. Allowed was adjunctive treatment with clonazepam 0.5 mg four times daily as needed, clonidine 0.1 mg every four hours as needed (max 1.2 mg/day); trazodone 100 mg every night at bedtime, zolpidem 10 mg every night at bedtime, and prochlorperazine 10 mg PO three times daily.

Available evidence suggests that naltrexone-accelerated withdrawal can achieve a higher rate of induction onto LAI-NTX in fewer days compared with other approaches:

- A meta-analysis comparing use of alpha-2 agonist treatment alone compared with alpha-2 agonist combined with opioid antagonists indicated naltrexone-accelerated protocols may have some advantages, but overall the data are too limited to recommend one approach over another [61].

- An outpatient clinical trial randomly assigned 150 patients with DSM-IV opioid dependence to undergo naltrexone-accelerated withdrawal over seven days or a seven-day taper of buprenorphine followed by a one-week wait [65]; induction onto LAI-NTX was then attempted for both groups. More patients in the naltrexone-accelerated group were successfully inducted onto LAI-NTX compared with the buprenorphine taper group (56 versus 33 percent). No difference in COWS or Hamilton Depression Rating scores were observed.

- A randomized clinical trial examined a seven-day outpatient detoxification and transition to LAI-NTX study comparing three groups: oral naltrexone induction from day 1 plus sublingual buprenorphine taper, placebo naltrexone plus sublingual buprenorphine taper, or placebo naltrexone plus placebo sublingual buprenorphine taper. Ancillary medications were used to manage withdrawal symptoms, including clonidine, trazadone, and clonazepam. All three groups showed similar rates of induction onto intramuscular naltrexone (47, 41, 47 percent respectfully); however, this protocol involved initiation of very low doses of naltrexone (as low as 0.25 mg naltrexone) at the start of detoxification [66]. Subjects in the active oral naltrexone group were significantly more likely to remain abstinent during the seven-day detoxification period than those in the other two groups (odds ratio = 1.54; 95% CI 1.31-1.80). On day 9, when transition to LAI-NTX was done, the

active oral naltrexone group had significantly lower COWS scores than subjects in the other two groups. The study supports the utility of rapid induction onto naltrexone while conducting the buprenorphine taper.

Ultra-rapid or anesthesia-assisted opioid withdrawal — "Ultra-rapid" opioid withdrawal involves use of heavy sedation and intravenous infusion of high-dose naloxone to shorten physiologic detoxification to as little as eight hours [67,68].

We recommend that this approach **not** be used, consistent with recommendations of the American Society of Addiction Medicine [27] and the National Institute for Health and Care Excellence consortium in England [58]. A meta-analysis of multiple clinical trials [69] of antagonist-induced withdrawal with heavy sedation/anesthesia did not influence the intensity or duration of the withdrawal but had a greater risk of adverse events compared with light sedation (risk ratio 3.21, 95% CI 1.13-9.12). Serious complications including death have been reported [69-72].

Acupuncture — Acupuncture, when combined with opioid-agonist taper, may have some efficacy in reducing withdrawal symptoms. A meta-analysis of 11 clinical trials with 1105 opioid-dependent patients found some evidence suggesting that the combination of acupuncture and opioid taper reduced withdrawal symptoms in comparison with opioid taper alone [73]. Caution should be used in interpreting these findings due to methodologic limitations and differences across trials (eg, in the kind of acupuncture, opioid tapering strategies, and opioid withdrawal scales).

The National Acupuncture Detoxification Association auricular protocol has shown some efficacy in reducing anxiety associated with supervised withdrawal [74].

Other — In addition to methadone, other long-acting opioid agonists such as tramadol extended-release have shown efficacy in tapering opioids to avoid withdrawal [75-77]. A meta-analysis of tramadol efficacy did not support a significant difference from either known treatments or placebo [78].

Other medications have been studied in small trials or case reports, either alone or combined with methadone taper, including gabapentin [79,80], pregabalin [81], N-methyl-D-aspartate agonists [82-84], methadone taper combined with very low-dose naltrexone (eg, 0.125 or 0.25 mg) [85,86], ondansetron, a 5-HT3a agonist [87], venlafaxine [88], buspirone [89], buspirone plus buprenorphine [90], dronabinol [91], and cannabinoid-1 receptor (CB1)-agonists [92]. The evidence for these interventions is currently insufficient for us to conclude that they are efficacious or suggest their use in clinical practice.

Kratom — Kratom (*Mitragyna speciosa*), an herb with opioid and stimulant-like properties, contains indole alkaloids, principally mitragynine and 7-HO-mitragynine, with mu-opioid receptor agonism [93]. It has been used for self-treatment of opioid withdrawal, with little published evidence of efficacy and increasing numbers of reports of lethal overdose and other adverse effects [93,94]. Kratom should **not** be used in patients withdrawing from opioids.

Investigation of kratom's efficacy and toxicity is limited to case reports/series [93]. In higher doses of 5 to 15 g, frequent and prolonged ingestion of kratom for pain or recreational use has been associated with respiratory depression, anorexia, weight loss, seizures, depression, psychosis, physiologic tolerance, and withdrawal (similar to that seen with opioids) [95]. Opioid withdrawal symptoms emerge 12 to 24 hours after last use and persist for up to seven days. Naltrexone administration can induce precipitated withdrawal in those physiologically dependent on kratom [96]. There are no controlled trials supportive of specific pharmacologic treatment of kratom withdrawal, but a 2019 review suggested treatment similar to withdrawal from other opioids, specifically alpha-2-adrenergic agonists and symptomatic treatment [97].

Kratom use is prohibited in some countries and states in the United States. The FDA has issued multiple advisories on kratom: on health risks with its use for opioid withdrawal [98], its association with a multistate *Salmonella* outbreak in 2018 [99], and on a mandatory recall of kratom-containing products associated with Triangle Pharmanaturals, LLC in 2018 [100].

Fentanyl and derivatives — The rapid rise in high potency synthetic opioid exposure, especially fentanyl, means that in many regions the majority of heroin is laced with fentanyl, and fentanyl has become the deadliest agent implicated in opioid overdose death in the United States [101]. Those misusing opioid pain medications increasingly are exposed to fentanyl in tablets believed to be a lower potency opioid (eg, oxycodone) [102]. Fentanyl and fentanyl derivatives have higher affinities and potencies at the mu opioid receptors than the natural and semi-synthetic opioids, though not buprenorphine [103].

The high lipophilicity of fentanyl results in a slow redistribution from tissues back into the plasma. Thus, not only is respiratory suppression more prolonged after overdose, necessitating rapid and repeated administration of naloxone, but the time course of withdrawal is more difficult to predict. There are no controlled trials examining withdrawal from fentanyl. As one might predict from the affinity differences, it is commonly held that standard treatment approaches, such as buprenorphine substitution, might not be as effective in those dependent on fentanyl [104]. However, this is far from established, and standard induction approaches need not be abandoned based on current evidence [105]. Establishing guidance on use of standard withdrawal treatment protocols or using low-dose or high-dose buprenorphine inductions, is in its infancy [106].

Opium — In opium producing countries and their neighbors, especially Afghanistan, Iran, Myanmar, and Laos, opium use can be more common than that of other opioids [107]. Withdrawal symptoms from opium are similar to those with other substances, though often milder, with peak symptoms at days 2 to 4. A 2018 meta-analysis of 13 trials in Iran, India, and Thailand did not include any studies comparing active compound with placebo [108]. Studies were either of low or very low quality, and no specific pharmacologic therapies were supported. Overall, treatment of opium withdrawal is likely to be similar to that for other opioids.

COMPLICATIONS

Withdrawal precipitated by buprenorphine and/or a full antagonist like naltrexone is often quicker in onset and more severe than spontaneous withdrawal. Complications can require hospitalization; even intensive care unit admissions have been described [109]. Cases of organic delusional syndromes [110] and stress cardiomyopathy [111,112] have been reported, resulting from both precipitated and spontaneous withdrawal. Seizures are rare (except in withdrawal from meperidine) and may indicate concurrent withdrawal from alcohol or benzodiazepines, or a preexisting seizure diathesis. Severe nausea and vomiting with dehydration may require aggressive intravenous rehydration and correction of electrolyte abnormalities on a medical unit.

Patients undergoing opioid withdrawal are at risk of suicide, driven by the psychic distress and fear that often accompanies opioid withdrawal and/or feelings of failure among patients unable to complete the process. Patients should be assessed for suicidality throughout supervised withdrawal, with positive findings resulting in clinically appropriate increases in the level of observation and follow-up. (See "Suicidal ideation and behavior in adults".)

Another significant risk associated with medically supervised withdrawal is unintentional overdose, often a result of a sequence of events:

- Patient elopement during supervised withdrawal.
- Resumption of opioid use in the context of severe craving and desire to ameliorate remaining withdrawal symptoms.
- Opioid overdose of patient who resumed use at their prewithdrawal “dose.” They are at increased risk of respiratory depression and death due to the loss of tolerance to opioids over the course of supervised withdrawal.

Patients should be warned multiple times of the risks associated with decreased opioid tolerance; they and family or coresidents should be provided take-home naloxone and education on its use [113]. (See 'Continuing care' below and "Prevention of lethal opioid overdose in the community".)

CONTINUING CARE

Medically supervised withdrawal is a first step in a long process of maintaining abstinence [27,114]. High rates of relapse in the month following supervised withdrawal are the norm if withdrawal is not followed by the patient's successful transition to maintenance treatment [29]. Collaboration between the patient and their clinicians on a treatment plan to follow withdrawal is key to maximizing chances of longer-term success [115,116]. Clinicians participating in supervised withdrawal should aim to develop a therapeutic alliance with the patient, work to build their motivation, and emphasize the need for long-term treatment [58] that includes:

- Pharmacotherapy and psychosocial interventions.
  - (See "Opioid use disorder: Psychosocial management" and "Opioid use disorder: Pharmacologic management" and "Substance use disorders: Principles, components, and monitoring during treatment with contingency management" and "Substance use disorders: Training, implementation, and efficacy of treatment with contingency management" and "Substance use disorders: Motivational interviewing".)
  - (See "Opioid use disorder: Psychosocial management" and "Opioid use disorder: Pharmacologic management" and "Substance use disorders: Principles, components, and monitoring during treatment with contingency management" and "Substance use disorders: Training, implementation, and efficacy of treatment with contingency management" and "Substance use disorders: Motivational interviewing".)
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- (See "Opioid use disorder: Psychosocial management" and "Opioid use disorder: Pharmacologic management" and "Substance use disorders: Principles, components, and monitoring during treatment with contingency management" and "Substance use disorders: Training, implementation, and efficacy of treatment with contingency management" and "Substance use disorders: Motivational interviewing".)

- An intensity of treatment and monitoring with urine drug testing appropriate to the patient's clinical status and risk of relapse. (See "Continuing care for addiction: Components and efficacy" and "Continuing care for addiction: Implementation".)

- Education about decreased opioid tolerance and overdose risks; take-home naloxone and education about its use for overdose [113]. (See "Prevention of lethal opioid overdose in the community".)

CLINICIAN EDUCATION AND TRAINING

The Substance Abuse and Mental Health Services Administration-funded Providers' Clinical Support System for Medication Assisted Treatment (PCSS) in the United States provides training and educational materials for clinicians using opioid agonists and antagonists for medically supervised opioid withdrawal and maintenance treatment. PCSS provides clinicians with access to a nationwide network of mentors for prescribing clinicians who are unfamiliar with treatment for patients with opioid use disorders.

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

- **Indications and contraindications** – Medically supervised opioid withdrawal, also known as detoxification, involves the administration of medication to reduce the severity of withdrawal symptoms that occur when a patient with physiological dependence on opioids stops using opioids. Its principal purpose is to safely and successfully transition the patient to subsequent, continuing treatment to maintain abstinence from illicit opioids. (See 'Introduction' above and 'Indications and contraindications' above.)

We agree with the with the recommendation of the American College of Obstetricians and Gynecologists that individuals who are pregnant with opioid use disorder start or continue medication for opioid use disorder with an opioid agonist or partial agonist during pregnancy rather than undergo medically supervised withdrawal and attempt to maintain abstinence. Some women may refuse opioid-agonist maintenance treatment in favor of medically supervised withdrawal. (See 'Indications and contraindications' above and "Opioid use disorder: Overview of treatment during pregnancy" and "Opioid use disorder: Pharmacotherapy with methadone and buprenorphine during pregnancy".)

- **Monitoring** – We use the Clinical Opioid Withdrawal Scale (COWS), a structured instrument with a standardized scoring system in conjunction with clinical observation to assess the progress and severity of withdrawal, and guide medication administration. We prefer the COWS because of its ease of use and sensitivity and it is found on the associated table (table 1). (See 'Monitoring' above.)

- **Treatment preferences** – For most patients with physiologic dependence on opioids undergoing medically supervised withdrawal, we suggest first-line treatment with buprenorphine-naloxone rather than methadone or an alpha-2 adrenergic agonist (**Grade 2B**). If buprenorphine is unavailable or unfamiliar, methadone is a reasonable alternative, provided that the patient is in a closely monitored inpatient or residential setting that can minimize risk of overdose/diversion and the patient lacks cardiac or other contraindications to its use. (See 'Buprenorphine-naloxone' above and 'Methadone' above.)

  For patients in settings that prohibit use of controlled substances including opioid agonists (eg, drug-free residential programs, prisons), we suggest use of an alpha-2 adrenergic medication such as clonidine for supervised withdrawal compared with no pharmacologic treatment (**Grade 2B**). (See 'Alpha-2 adrenergic agonists' above.)

- **Adjunctive medication** – We use symptom-specific adjunctive medications (also known as symptomatic treatment) to provide targeted relief of withdrawal symptoms (eg, cramping, diarrhea, nausea) that occur despite primary-medication treatment (table 2). There are several options for each symptom type. Our first-line preferences are noted on the table. (See 'Adjunctive medications' above.)

- **Ultra-rapid or anesthesia-assisted opioid withdrawal** – We recommend that "ultra-rapid" or anesthesia-assisted withdrawal **not** be used in medically supervised opioid withdrawal (**Grade 1B**). (See 'Ultra-rapid or anesthesia-assisted opioid withdrawal' above.)

- **Suicide** – We assess for suicidality throughout the course of supervised withdrawal. Patients undergoing opioid withdrawal are at risk of suicide, driven by the psychic distress

and fear that often accompanies withdrawal and/or feelings of failure among patients unable to complete the process. (See 'Complications' above.)

- **Continuing care** – Medically supervised withdrawal is a first step in a long process of maintaining abstinence from illicit use of opioids. High rates of relapse in the month following supervised withdrawal are the norm if withdrawal is not followed by the patient's successful transition to maintenance treatment. (See 'Continuing care' above.)

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