Approach to treating opioid use disorder

Authors: Andrew J Saxon, MD, Eric Strain, MD, K Michelle Peavy, PhD, MAC
Section Editor: Richard Saitz, MD, MPH, FACP, DFASAM
Deputy Editor: Michael Friedman, MD

All topics are updated as new evidence becomes available and our peer review process is complete.

Literature review current through: Jul 2021. | **This topic last updated:** May 05, 2021.

INTRODUCTION

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

First-line treatment for most patients with opioid use disorder most commonly consists of pharmacotherapy with an opioid agonist or antagonist and adjunct psychosocial treatment. Some patients prefer psychosocial treatment alone without medication.

Our approach to selecting treatment for opioid use disorder is described in this topic (algorithm 1). Specific medications and psychosocial treatments for opioid use disorder are reviewed separately with information on their efficacy, side effects, and administration. The epidemiology, pharmacology, clinical manifestations, course, assessment, and diagnosis of opioid use disorder are also reviewed separately. Medically supervised opioid withdrawal is also reviewed separately, as is misuse of prescribed medications including opioids:

- (See "Pharmacotherapy for opioid use disorder".)
- (See "Psychosocial interventions for opioid use disorder".)
- (See "Opioid use disorder: Epidemiology, pharmacology, clinical manifestations, course, screening, assessment, and diagnosis".)
- (See "Medically supervised opioid withdrawal during treatment for addiction".)
- (See "Prescription drug misuse: Epidemiology, prevention, identification, and management".)

Shared decision-making — Selecting treatment for opioid use disorder involves making choices (eg, between opioid agonists and antagonists), which should be made on the basis of shared decision-making between the provider and the patient (and may also include family members). Patients should be educated about the potential advantages and disadvantages of each treatment option. A discussion between the clinician and patient will typically be necessary to make initial and/or subsequent choices.

A systematic review of 24 clinical trials with 8728 patients with substance use disorder provided some support for involving patients in making decisions about the treatment process [1]. As an example, in a trial of 3103 patients with substance use disorder seeking treatment (a proportion of which were primary heroin users), a higher percentage of patient-reported needs matched to services improved drug use outcomes at one-year follow-up [2].

Opioid use disorder in DSM-5 — Most clinical trials on the efficacy of treatments for opioid use disorder studied patients with an American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) diagnosis of opioid dependence. Applying these findings to patients diagnosed under the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) is imprecise, but the most closely comparable group of patients is those with opioid use disorder, moderate to severe subtype (ie, patients with four or more diagnostic criteria within a 12-month period). DSM-5 criteria for the diagnosis of opioid use disorder are described separately. (See "Opioid use disorder: Epidemiology, pharmacology, clinical manifestations, course, screening, assessment, and diagnosis", section on 'Diagnosis'.)

INITIAL TREATMENT

For a patient newly diagnosed with opioid use disorder, initial treatment is selected based on the patient's clinical status including disorder severity, risk of relapse, patient preference, family input (if indicated), and the current evidence base. For patients with a history of previous treatment episodes, the person's history of response to prior treatments also can be informative.

Medically supervised opioid withdrawal — Regular opioid users become physiologically dependent on the drug and experience withdrawal symptoms following its abrupt termination. Medically supervised opioid withdrawal, also known as detoxification, reduces withdrawal symptoms as a first step in treatment. Medically supervised opioid withdrawal is not recommended as a standalone treatment. Subsequent treatment with medication (also known as "medication-assisted treatment" or "medication for addiction treatment" [MAT]) or psychosocial treatment is typically needed to prevent relapse.

Withdrawal from opioids should be fully completed before naltrexone (an opioid antagonist) is started, while methadone and buprenorphine (referred to here as opioid agonists, although technically buprenorphine is a partial agonist) can be started for a person currently using opioids or before withdrawal is completed. (See "Opioid withdrawal in adults: Clinical manifestations, course, assessment, and diagnosis" and "Medically supervised opioid withdrawal during treatment for addiction".)

Medically supervised opioid withdrawal may increase some patients' risk of overdose given the high rate of relapse in people who use opioids combined with lowered physiological tolerance following supervised withdrawal.

A naloxone challenge test can be performed to ensure that the patient is no longer physically opioid dependent before starting naltrexone. (See "Pharmacotherapy for opioid use disorder", section on 'Naloxone challenge test'.)

Selecting MAT versus psychosocial treatment alone — For most patients with moderate to severe opioid use disorder we recommend first-line treatment with medication (MAT) rather than psychosocial treatment alone. Psychosocial treatment alone can be used if the patient has history of a prior sustained response, or if the person has a mild disorder, is highly motivated for treatment, and has good premorbid functioning and strong psychosocial supports, or if the patient has a strong preference for psychosocial treatment alone despite education on the superior efficacy of MAT. (See 'Patient preference' below and 'Psychosocial treatment alone' below.)

Many clinical trials have shown MAT [3-5] to reduce substance use compared with placebo in patients with opioid use disorder, while fewer trials have found psychosocial treatment alone [6-8] to be efficacious compared with control conditions (see "Pharmacotherapy for opioid use disorder" and "Psychosocial interventions for opioid use disorder"). Most clinical trials that directly comparing these modalities in patients with opioid use disorder have found MAT to result in reduced substance use and greater rates of abstinence compared with psychosocial treatment alone [9,10]:

As an example, a clinical trial randomly assigned 40 patients with the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) opioid (heroin) dependence to daily buprenorphine or placebo for 12 months [10]. Both groups received a combination of group cognitive-behavioral therapy (CBT) and individual counseling sessions. At the end of the study, one-year retention in treatment was 75 versus 0 percent in the buprenorphine and placebo groups, respectively (risk ratio 58·7 [95% CI 7.4–467.4]). Urine

screens were about 75 percent negative for opioids and other common illicit substances in the patients remaining in treatment.

Patient preference — Despite education about research findings and clinical experience establishing the superiority of MAT, some patients prefer nonmedication psychosocial treatment. Provided the patient is well informed about risks and benefits and is armed with the information that medication offers some protection against overdose, the person's choice should be supported, and the patient can be reoffered MAT if nonmedication treatment is not effective. (See 'Psychosocial treatment alone' below.)

Medication for addiction treatment — MAT for opioid use disorder consists of treatment with an opioid agonist or opioid antagonist, typically accompanied by psychosocial treatment. MAT with buprenorphine [3], methadone [4], or naltrexone [5] has been found to be safe and efficacious compared with placebo in the treatment of opioid use disorder. The severity of opioid use disorder and other factors influencing treatment selection for the disorder are reviewed below, followed by subgroups warranting special consideration. (See 'Subgroups with special needs' below and "Pharmacotherapy for opioid use disorder".)

Regulation in the United States — Methadone and buprenorphine are regulated as controlled substances (schedule II and schedule III drugs, respectively) in the United States, establishing different requirements and settings for administering each drug. Thus, the choice between the two medications can also be a choice between treatment environments and patient experiences. One or the other may be better suited or preferred by certain patients.

Regulations require methadone to be dispensed to outpatients at licensed opioid treatment programs (OTP), highly regulated treatment environments that provide counseling and social services. Medication is typically dispensed daily for patients in an initial phase of treatment. OTPs are designed to serve larger numbers of individuals with opioid use disorder.

While buprenorphine may also be dispensed in OTPs, patients can receive buprenorphine prescribed in an office-based practice. Such settings require prescriber training and certification; the practice must indicate that they have the capacity to provide or to refer patients for counseling. Access to a sufficient number of prescribers may be an issue in some regions. (See "Pharmacotherapy for opioid use disorder", section on 'Regulation of buprenorphine in United States' and "Pharmacotherapy for opioid use disorder", section on 'Regulation of methadone in United States'.)

First-line medication for moderate to severe disorder — For MAT-treated patients with moderate to severe opioid use disorder, we suggest buprenorphine as the first-line medication rather than methadone or naltrexone. Methadone is a reasonable alternative in patients with a

history of a poor response to buprenorphine, previous misuse or diversion of buprenorphine, with higher levels of opioid physical dependence (eg, as indicated by more severe withdrawal symptoms when stopping opioids, and/or fulfilling a greater number of Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition [DSM-5] opioid use disorder criteria), or who have had previous treatment with methadone and prefer this medication.

For patients who decline agonist treatment and who have completed or can complete full withdrawal from opioids, long-acting injectable (LAI) naltrexone is a reasonable alternative treatment. For highly motivated patients who prefer to avoid both injections and agonist treatment and who have completed or can complete withdrawal, oral naltrexone taken daily under supervised conditions would be a reasonable alternative. (See "Pharmacotherapy for opioid use disorder", section on 'Naltrexone'.)

Our selection among these medications is based on their relative safety and efficacy in clinical trials (described below) and in our clinical experience. Clinical trials comparing agonists versus an antagonist, and buprenorphine versus methadone are reviewed below. An algorithm describes our approach to selecting medications for treatment of opioid use disorder (algorithm 1) (see "Pharmacotherapy for opioid use disorder"):

- **Opioid agonists versus antagonists –** For most patients with moderate to severe opioid use disorder, we favor first-line treatment with opioid agonists rather than antagonists.

  We generally favor opioid agonists as first-line treatment because many studies, like this one [11], have found that a significant proportion of patients cannot surmount the challenge of completing the full withdrawal from opioids required prior to treatment with naltrexone. However, these studies do show that for patients who can complete full withdrawal, LAI naltrexone achieves outcomes equivalent to those achieved with buprenorphine. For that select group of patients, LAI naltrexone is a reasonable first-line treatment.

  Two clinical trials have compared monthly LAI naltrexone with daily transmucosal buprenorphine, finding little evidence of a difference in abstinence rates, although it appears that initial stabilization on buprenorphine may be easier to accomplish. The trials did not compare efficacy between subgroups based on treatment motivation or disorder severity (see "Pharmacotherapy for opioid use disorder", section on 'Opioid agonists' and "Pharmacotherapy for opioid use disorder", section on 'Opioid antagonists'):

  - An open-label clinical trial comparing monthly LAI naltrexone and daily transmucosal buprenorphine found the two medications to be comparably effective in reducing the use of heroin and other illicit opioids in formerly opioid-dependent patients who had

subsequently been incarcerated, hospitalized, or had completed medically supervised opioid withdrawal [12]. This open-label trial randomly assigned 159 adult participants to receive transmucosal buprenorphine-naloxone (4 to 24 mg/day) or LAI naltrexone (380 mg administered intramuscularly every four weeks) for 12 weeks. At the end of the trial, LAI naltrexone was noninferior to buprenorphine in the proportion of opioid-negative urine drug tests and in days of heroin or other illicit opioid use.

- An open-label clinical trial randomly assigned 570 patients with opioid use disorder to receive monthly LAI naltrexone or daily transmucosal buprenorphine (mean maintenance dose 16 mg/day [interquartile range 12 to 18 mg]) for 24 weeks [11]. The patients had entered inpatient programs for planned withdrawal from opioids but had not necessarily completed withdrawal at the time of enrollment. A smaller proportion of participants assigned to the naltrexone group were successfully inducted onto medication compared with the buprenorphine group (72 versus 94 percent).

  In the intent to treat sample, because of the disparity in induction success, a greater proportion of participants assigned to naltrexone relapsed to regular opioid use compared with participants assigned to buprenorphine (65 versus 57 percent). However, among the 474 participants successfully inducted onto medication, relapse rates did not differ between the two groups (52 versus 56 percent).

- Buprenorphine **versus** methadone **–** We favor buprenorphine first line rather than methadone in patients with opioid use disorder. Although available data suggest that methadone is on average slightly more efficacious than buprenorphine, in most clinical circumstances, buprenorphine is safer than methadone. Clinical trials comparing the two medications are summarized below. Efficacy compared with placebo, adverse effects, and administration including dosing are reviewed separately. (See "Pharmacotherapy for opioid use disorder", section on 'Buprenorphine' and "Pharmacotherapy for opioid use disorder", section on 'Methadone'.)

  - **Efficacy –** A meta-analysis of 11 randomized trials comparing methadone to buprenorphine in maintenance treatment for DSM-IV opioid dependence concluded that buprenorphine was effective in opioid use disorder but slightly less effective than methadone in its capacity to retain patients in treatment [3].

    As an example, a trial comparing buprenorphine (maximum daily dose 8 mg transmucosal) with methadone maintenance (up to 80 mg) found that more patients receiving methadone continued therapy [13]. However, of patients who completed the study, those taking buprenorphine had significantly lower rates of illicit opioid

consumption. Similar results have been reported by others, suggesting that maintenance with this agent may be most useful in highly motivated patients [14].

- **Risk of overdose –** Methadone has significantly higher risks of misuse and lethal overdose compared with buprenorphine [15,16]. Buprenorphine, as a partial opioid agonist, has a much lower potential for causing respiratory depression. Methadone doses used for opioid use disorder 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. Unlike buprenorphine, methadone requires essentially daily clinic-based treatment with observed ingestion during the initial treatment period.

  As an example, a nonrandomized, retrospective study of 16,434 individuals with a DSM-IV diagnosis of opioid dependence and treated with medication showed a fourfold greater rate of mortality from overdose associated with methadone treatment compared with buprenorphine [16].

  Individuals treated with either methadone or buprenorphine should be provided overdose education and naloxone distribution. (See "Prevention of lethal opioid overdose in the community".)

Further information on the efficacy and safety of buprenorphine and methadone for opioid use disorder compared with placebo, their pharmacology, adverse effects, and administration including dosing are reviewed separately. (See "Pharmacotherapy for opioid use disorder", section on 'Buprenorphine' and "Pharmacotherapy for opioid use disorder", section on 'Methadone'.)

First-line medication for mild opioid use disorder — For most patients with a mild opioid use disorder who will be receiving MAT and who are highly motivated for treatment, we suggest first-line treatment with LAI naltrexone (administered monthly) rather than an opioid agonist. Oral naltrexone (administered daily, optimally under supervision) is a reasonable alternative for highly motivated patients who refuse injections or have good external support. Psychosocial treatment alone is a reasonable alternative for highly motivated patients who prefer nonmedication treatment, but since naltrexone is a generally safe and well-tolerated medication, working with such patients to encourage its use is advisable. (See "Pharmacotherapy for opioid use disorder", section on 'Naltrexone' and 'Psychosocial treatment alone' below.)

Mild opioid use disorder has not been well studied; almost all trials of opioid use disorder treatment included only patients with a moderate to severe opioid use disorder (see 'Opioid use

disorder in DSM-5' above). Treatment decisions for mild opioid use disorder are based upon our clinical experience.

Naltrexone as the initial treatment choice for mild opioid use disorder 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 opioid use disorder, naltrexone does not risk creating physiologic dependence when none currently exists.
- Patients with mild opioid use disorder with no withdrawal symptoms could be placed on a few days of oral naltrexone followed by LAI naltrexone. If a patient with mild opioid use disorder has a poor response or unacceptable side effects with naltrexone, it is easy to switch to methadone or buprenorphine, but 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 DSM-IV opioid dependence in randomized trials [17-20]. Oral naltrexone has been found to be effective compared with placebo when adherence is enforced [5]. Further information on the efficacy of naltrexone for opioid use disorder compared with placebo, its pharmacology, adverse effects, and administration are reviewed separately. (See "Pharmacotherapy for opioid use disorder", section on 'Naltrexone'.)

Adjunctive psychosocial treatment — We suggest individual or group substance use disorder counseling for patients receiving MAT for opioid use disorder. The recommendation is to offer available psychosocial support and encourage, but not require, the patient to engage. Some evidence suggests that patients receiving MAT who are given a choice about counseling will voluntarily attend counseling about as often as those for whom counseling is required [21], demonstrating that patients may value the option of counseling when empowered to choose it themselves. (See "Psychosocial interventions for opioid use disorder".)

Across substance use disorders, contingency management is the psychosocial treatment that consistently shows the best evidence for producing outcomes reducing substance use [22]. This intervention involves the use of incentives as positive reinforcement for target behaviors such

as substance use (as measured by drug screening) or treatment attendance. (See "Psychosocial interventions for opioid use disorder", section on 'Contingency management'.)

In some circumstances, psychosocial treatments may not be available or acceptable to the patient. We do not recommend withholding medication in the absence of psychosocial treatment. Even a suboptimal response to pharmacotherapy may reduce morbidity and mortality.

Rationale for adjunctive psychosocial treatment — Despite the mixed results from trials adding psychosocial interventions to medication treatment, we encourage patients with opioid use disorder to participate in evidence-based psychosocial interventions. This is particularly true when only a partial response is obtained from medication. 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. (See 'Ambivalence and ongoing opioid use' below and 'Selecting among psychosocial interventions' below.)

Efficacy for augmentation of pharmacologic treatment with psychosocial treatment for opioid use disorder is mixed. Additionally, due to heterogeneity of treatments and small sample sizes, there is limited empirical evidence on the specific type of psychosocial treatment that is most effective in combination with specific medication treatments. Further research is needed regarding differential effectiveness of the various psychosocial approaches combined with medical treatments and their effects on different patient populations and settings. (See "Psychosocial interventions for opioid use disorder".)

As an example, a systematic review examined the use of psychosocial interventions combined with medication versus control conditions or standard treatment in individuals with opioid use disorder [23]. Psychosocial interventions included contingency management, CBT, behavioral drug counseling, motivational interviewing, and acceptance and commitment therapy. Outcomes measures including treatment retention and illicit drug use generally supported the use of psychosocial interventions for each pharmacologic treatment but were quite variable across studies, outcomes, medications, and psychosocial interventions.

Individual clinical trials comparing medication treatment with psychosocial augmentation versus medication treatment alone have found mixed results [24-28]. As examples:

- In a trial 653 treatment-seeking outpatients with prescription opioid dependence were randomly assigned to standard medical management with buprenorphine-naloxone versus standard management plus opioid dependence counseling [29]. The trial did not demonstrate a difference in success rates (composite measures indicating minimal or no

opioid use based on urine test confirmed self-reports) between standard medical treatment and standard medical treatment plus opioid dependence counseling.

- A clinical trial randomly assigned 230 adults with opioid dependence to be treated with methadone for 12 months and to additionally receive for the first four months: emergency counseling only, routine counseling, or routine counseling with smaller counselor caseloads [24]. At 12 months, there were no significant differences among groups in treatment retention (60.6 versus 54.8 and 37.8 percent, respectively) or urine tests results positive for opioids.

- In a small trial, 41 young adults in inpatient/residential treatment for opioid use disorder were randomly assigned to assertive treatment including family engagement, assertive outreach, contingency management, and home delivery of LAI opioid antagonist (XR-naltrexone) versus control (referral to outpatient care). By the end of the 24-week treatment period, participants in the assertive treatment group received a greater number of treatment doses (mean 4.28 versus 0.7) and had lower rates of returning to use (61 versus 95 percent) than those in the control group. Additionally, survival analyses at 24 weeks showed participants in the control group were more likely to relapse (defined as ≥10 days of use within 28 days) sooner versus those in the assertive treatment group (hazard ratio 2.72, 95% CI 1.25-5.88) [28].

Subgroups with special needs

Ambivalence and ongoing opioid use — For patients with opioid use disorder who continue to use illicit opioids or do not participate in treatment, we favor motivational interviewing, an intervention that has been found to reduce substance use in patients with substance use disorder [30]. Components of motivational interviewing, its efficacy, and its administration for substance use disorders and for opioid use disorder are reviewed separately. (See "Motivational interviewing for substance use disorders" and "Psychosocial interventions for opioid use disorder", section on 'Motivational interviewing'.)

Nonadherence — For patients with nonadherence to daily doses of buprenorphine or oral naltrexone, supervised medication taking can be tried. If there are problems with adherence for these daily dose forms, we suggest treatment with LAI naltrexone or a long-acting subcutaneous buprenorphine. (See "Pharmacotherapy for opioid use disorder" and "Pharmacotherapy for opioid use disorder", section on 'Buprenorphine'.)

Clinical trials have found longer-acting formulations of naltrexone to reduce heroin use compared with the oral formulation [31,32]. A trial compared a single administration of a naltrexone implant (2.3 g; plus placebo pill) with oral naltrexone (50 mg/day) for six months in

70 patients with heroin dependence [32]. Patients receiving naltrexone implants were less likely to have returned to regular heroin use by six months and returned later to such use (158 versus 115 days) compared with patients receiving oral naltrexone. A randomized clinical trial comparing oral with LAI naltrexone demonstrated that the latter is superior [31]. Longer-acting formulations of buprenorphine [33-35] and naltrexone [17-20] have both been found to be more effective than placebo for DSM-IV opioid dependence in randomized trials. The efficacy, adverse effects, and administration of the long-acting medications are reviewed separately. (See "Pharmacotherapy for opioid use disorder", section on 'Buprenorphine' and "Pharmacotherapy for opioid use disorder", section on 'Long-acting injectable naltrexone'.)

Safety sensitive occupations/criminal justice settings — In areas such as public safety, transport of hazardous materials, commercially licensed drivers, and health care, some employees are not allowed to use methadone or, in some cases, buprenorphine. These medications are not available in many prisons and other criminal justice settings.

Pregnancy — Both methadone and buprenorphine are effective pharmacotherapies for opioid use disorder in pregnancy and neither appears to be teratogenic [36]. For the mother, buprenorphine may pose a lower risk of mortality from overdose compared with methadone [16,37]. (See "Overview of management of opioid use disorder during pregnancy" and "Methadone and buprenorphine pharmacotherapy of opioid use disorder during pregnancy".)

Opioid withdrawal and treatment with an opioid antagonist is not considered first-line treatment for pregnant women with opioid use disorder because we lack 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 [38]. Observational studies do not find substantially worse outcomes for either mothers or neonates among women treated with naltrexone versus methadone or buprenorphine [39,40]. Although it remains controversial, we suggest that for women who become pregnant while taking naltrexone for opioid use disorder and are doing well on the medication, that it be continued. (See "Overview of management of opioid use disorder during pregnancy".)

Hospitalization — If a patient receiving maintenance treatment with methadone or buprenorphine is hospitalized, eg, for a traumatic injury or medical illness, the daily dose should be continued throughout the hospitalization. The hospital clinician should contact the OTP or buprenorphine prescriber as quickly as possible to verify the patient's current dose and to arrange for continuation of treatment with the medication by that provider after discharge. For buprenorphine prescribed outside of a licensed OTP, the dose may be verified by using the state prescription drug monitoring program. If the clinic is not available to verify the methadone dose, a dose of 30 mg can generally be given to abort acute withdrawal signs and

symptoms until further information is available. Since buprenorphine at any dose is unlikely to cause respiratory depression, it can be continued at the dose reported by the patient until the actual dose can be verified.

Psychosocial treatment alone — Psychosocial treatment alone – also known as nonmedication treatment, drug-free treatment, or abstinence-based treatment – typically consists of multiple psychosocial services. In general, psychosocial treatment alone is considered to be inferior to MAT for most patients and is not suggested for first-line treatment of opioid use disorder (see 'Selecting MAT versus psychosocial treatment alone' above). However, psychosocial treatment alone can reasonably be used as an alternative to MAT in patients who prefer it to MAT despite education on evidence-based treatment and overdose risks or for patients who have a mild disorder, are highly motivated to participate in treatment, and have good psychosocial support.

Selecting among psychosocial interventions — The selection of psychosocial interventions for patients with opioid use disorder can be influenced by the patient's clinical presentation, treatment history, preferences, and treatment availability, which can vary. Although numerous psychosocial interventions have been shown to reduce substance use, efficacy trials comparing interventions have not been adequate to inform selection among them. The following principles inform our selection process:

- In general, we favor beginning psychosocial treatment alone with a multimodal program that includes addiction counseling weekly, participation in a mutual help group several times per week, and a psychosocial intervention shown to reduce substance use in clinical trials, such as CBT, contingency management, motivational interviewing, a community reinforcement approach, or a combined behavioral intervention. (See "Psychosocial interventions for opioid use disorder" and "Psychotherapies for substance use disorders".)

- Based on our clinical experience, and in the absence of empirical data, we favor informing selection among interventions by viewing the patient's presentation through the framework of the Readiness to Change model [41], whereby interventions are selected to address patient stage-based deficits. (See "Brief intervention for unhealthy alcohol and other drug use: Goals and components".)

  As examples:

  - Individuals in precontemplation or contemplation stages of change should be targeted with motivational interviewing to enhance motivation to change. (See "Motivational interviewing for substance use disorders".)

- Patients who are ambivalent about engaging with a mutual help group may benefit from one of the variants of 12-step facilitation. However, if patients are continuing to use opioids and/or other substances, explicitly reject the 12-step philosophy, or voice strong opposition to attending 12-step groups, providers should use caution in recommending 12-step facilitation or 12-step group attendance. A clinical trial testing 12-step facilitation with stimulant users indicated that this intervention is not particularly effective for those who continue to use, and in fact, the rate of stimulant use for nonabstinent stimulant users was higher in the experimental group versus the control group [42].

- Mutual help groups, if selected carefully, can be useful at any point in a person's treatment trajectory. Individuals in action or maintenance stages of change benefit by involvement in peer-supported recovery, as they can develop a sense of "giving back" and mentoring those whose recovery is less stable. (See 'Adjunctive psychosocial treatment' above and "Psychosocial interventions for opioid use disorder", section on 'Mutual help groups'.)

- Contingency management can target patients in the precontemplation/contemplation stages of change, especially when contingency management targets attendance. Contingency management can enhance engagement and further a person's overall motivation. (See "Contingency management for substance use disorders: Efficacy, implementation, and training".)

- Individuals in preparation or action stages of change would be better matched with action-orientated or skill building interventions, such as CBT and its variants, which leverage the desire to initiate or sustain behavior change. Multimodal CBT models incorporate additional objectives, such as attention to needs for social services in the community reinforcement approach. (See "Psychosocial interventions for opioid use disorder", section on 'Cognitive-behavioral therapy' and "Psychotherapies for substance use disorders", section on 'CBT-based therapies'.)

- To the extent that a patient is reliant on a specific clinician or team for his/her/their treatment, the selection of interventions will depend on the clinician/team's particular strengths and training, as well as the patient's needs.

RESPONSE TO INITIAL TREATMENT

Robust response — No controlled studies have evaluated the optimal length of time that patients should remain on medication for addiction treatment (MAT). There is no specific time frame of recommended treatment. For patients who are treatment responders and are satisfied to remain on MAT indefinitely, we support that strategy. For responders who wish to discontinue MAT and are fully free of problematic substance use, free of criminal activity, are spending time productively, and have stable interpersonal relationships, a taper of methadone or buprenorphine can be attempted. To be relatively confident that the patient is in that situation generally means at least 6 to 12 months of stability on medication treatment. If the patient becomes unstable with substance use, craving, withdrawal symptoms, or life stressors, the taper should be halted, and the patient encouraged to remain on medication until stability is again achieved.

For responders who wish to discontinue naltrexone, the medication can be stopped abruptly and patients followed carefully for any signs of instability. A lapse or relapse should prompt reinstitution of naltrexone treatment.

For the patient who responds to psychosocial treatment without MAT, we have no data to guide the choice of treatment length or intensity. An individualized treatment plan can be crafted for each patient with an overall plan to have at least some form of ongoing continuing care, which might be a mutual help group, and to consider some formal treatment contacts on a monthly or quarterly basis if that is acceptable to the patient and provider.

Continuing care — We recommend adoption of the continuing care model for addictions, which emphasizes that treatment for chronic or recurrent substance use disorders should be ongoing, not episodic, include routine monitoring during periods of abstinence as well as during exacerbation, and should adjust the intensity of treatment based on the patient's clinical status and risk of relapse. Continuing care is particularly important for opioid use disorder, which may be more chronic than other substance use disorders and often has a progressive trajectory. (See "Continuing care for addiction: Context, components, and efficacy" and "Continuing care for addiction: Implementation".)

Inadequate response — For patients with opioid use disorder who experience a poor response to MAT or psychosocial treatment alone, we suggest the following changes based on the patient's initial treatment. Our approach is based on our clinical experience; there are a lack of clinical trials comparing different sequences of medications for opioid use disorder following first-line treatment. (See 'Initial treatment' above.)

Opioid agonist — For patients with opioid use disorder who continue using illicit opioids despite first-line treatment with a maximally tolerated dose of buprenorphine or methadone,

we suggest second-line treatment with the alternative opioid agonist (ie, methadone or buprenorphine, respectively) (see "Pharmacotherapy for opioid use disorder", section on 'Opioid agonists'). For patients who initially received transmucosal buprenorphine, treatment with long-acting injectable (LAI) buprenorphine is a reasonable alternative. (See "Pharmacotherapy for opioid use disorder", section on 'Longer-acting'.)

For a patient initially started on buprenorphine and who has a poor response, it is easy to switch immediately to methadone treatment. For a patient initially started on methadone who has a poor response or unacceptable side effects, it can be difficult to switch to buprenorphine because several days off of methadone may be needed to avoid precipitated withdrawal when starting buprenorphine, depending upon the dose of methadone used.

For patients in treatment for a year or more who fail to stop using illicit opioids on a repeated and regular basis (eg nearly every urine drug screen is positive for illicit opioids) in response to optimal doses of opioid agonists **and** who can tolerate a week's-long period of medically supervised withdrawal and starting naltrexone without becoming dangerously unstable, we suggest treatment with LAI naltrexone (see "Pharmacotherapy for opioid use disorder", section on 'Long-acting injectable naltrexone'). For patients unable to tolerate the transition to naltrexone, continued treatment with the opioid agonist could be considered as part of a harm reduction strategy and could be combined with an intensification of psychosocial treatment and/or case management targeting specific patient needs (eg, housing, mental health). Motivational interviewing can be used to continue to prompt movement towards change in opioid use; this intervention can also target engagement in other recommended services.

Opioid antagonists — For patients who fail to stop using illicit opioids in response to treatment with naltrexone (either initial treatment with naltrexone or subsequent to an inadequate response to opioid agonist treatment), we suggest continuing naltrexone and increasing the intensity of psychosocial treatment.

Patients who do not respond to treatment with oral naltrexone should receive a trial with the LAI formulation if they have not already done so. Patients who do not respond to either formulation of naltrexone should be treated with buprenorphine.

Psychosocial treatment alone — For patients who fail to stop using illicit opioids on a repeated basis after 30 days of psychosocial treatment alone, we favor encouraging the initiation of MAT. If the patient declines MAT, we favor increasing the intensity of psychosocial treatment. Intensity may be increased by:

- Increasing the visit frequency.

- Increasing the level of care if available. (See "Determining appropriate levels of care for treatment of substance use disorders".)

- Adding another evidence-based psychosocial intervention (eg, adding contingency management to group addiction counseling). (See "Psychosocial interventions for opioid use disorder" and "Contingency management for substance use disorders: Theoretical foundation, principles, assessment, and components" and "Contingency management for substance use disorders: Efficacy, implementation, and training".)

Treatment-resistant MAT — For patients receiving medication for addiction treatment (MAT) for one year, and who continue to use illicit opioids on a regular and frequent basis (eg nearly every urine drug screen is positive for illicit opioids) despite adequate trials of agonist and antagonists, we favor increasing the intensity of psychosocial treatment. (See "Psychosocial interventions for opioid use disorder".)

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

As examples, cognitive-behavioral therapy can be substituted for addiction counseling or combined with contingency management. (See "Psychosocial interventions for opioid use disorder" and "Psychotherapies for substance use disorders".)

A stepped care approach, beginning treatment with buprenorphine and switching to methadone in patients with an inadequate response, yielded high rates of response in a clinical trial. Ninety-six patients with heroin dependence were randomly assigned to either stepped care or methadone; both groups additionally received behavioral therapy [43]. Buprenorphine was dosed at 16 mg at day 3, and titrated as needed to a maximum of 32 mg daily. Methadone was titrated to 70 mg by day 10, then to a maximum of 120 mg/day. A treatment retention rate of 78 percent was achieved in both groups, while the percentage of opiate-free urine samples ultimately reached approximately 80 percent.

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. PCSS provides clinicians with access to a nationwide network of mentors for prescribing clinicians who are unfamiliar with the treatment of opioid use disorders.

Many patients entering treatment for opioid use disorder lack access to formal, evidence-based psychosocial interventions but receive some form of counseling, whether by a counselor, medication prescriber, or dispensing nurse. We recommend that these health professionals, when aspiring to work with people who struggle with the disorder, acquire a baseline training in and understanding of motivational interviewing and the basic tenets of behavioral therapies. Motivational interviewing and behavioral therapies have both demonstrated some degree of efficacy in reducing opioid use. The motivational interviewing "way of being" provides a useful framework for understanding and approaching individuals with opioid use disorder. Counseling informed by these interventions should be offered to them as a matter of course. (See "Motivational interviewing for substance use disorders" and "Psychotherapies for substance use disorders", section on 'CBT-based therapies'.)

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

- Medication treatment for opioid use disorder consists of treatment with an opioid agonist (buprenorphine or methadone) or opioid antagonist (naltrexone) often augmented by psychosocial treatment. Patients with physiological dependence on opioids typically require medically supervised withdrawal before treatment with naltrexone; however, medically supervised withdrawal is not necessary prior to starting methadone or buprenorphine. (See 'Medication for addiction treatment' above and 'Medically supervised opioid withdrawal' above.)

- For most patients with moderate to severe opioid use disorder, we recommend medication for addiction treatment (MAT) first-line rather than psychosocial treatment alone (**Grade 1B**). (See 'Selecting MAT versus psychosocial treatment alone' above.)

- For most patients treated with MAT for a moderate to severe opioid use disorder, we suggest initial use of buprenorphine rather than methadone or naltrexone (**Grade 2C**). While methadone may have slightly better capacity to retain patients in treatment, it has a higher risk of lethal overdose. (See 'First-line medication for moderate to severe disorder' above.)

- For most patients with a mild opioid use disorder receiving MAT, we suggest first-line treatment with long-acting injectable (LAI) naltrexone (administered monthly) rather than other medications (**Grade 2C**). Oral naltrexone (taken daily) is a reasonable alternative for highly motivated patients whose medication taking is supervised. (See 'First-line medication for mild opioid use disorder' above.)

- For patients with opioid use disorder in safety-sensitive occupations or criminal justice settings that prohibit opioid agonist use, we suggest LAI naltrexone as first-line medication treatment rather than an opioid agonist (**Grade 2C**). (See 'Safety sensitive occupations/criminal justice settings' above.)

- For patients who are treated with medication for opioid use disorder, we suggest adjunctive treatment with addiction counseling and participation in a mutual help group such as Narcotics Anonymous (**Grade 2C**). Programs that dispense methadone in the United States (opioid treatment programs) are required to provide drug counseling. Clinicians who prescribe buprenorphine in an office-based practice are required to have the capability to provide or refer patients for drug counseling. (See 'Adjunctive psychosocial treatment' above.)

- Some patients are satisfied to remain on MAT indefinitely, while others wish to discontinue MAT. In a patient who is spending time productively and has stable interpersonal relationships – without problematic substance use, criminal activity – a taper of methadone or buprenorphine can be attempted. Naltrexone can be stopped abruptly. Patients should be followed carefully for any signs of instability. A lapse or relapse should prompt reinstitution of MAT. (See 'Robust response' above.)

- For patients with opioid use disorder who fail to stop using illicit opioids on a repeated and regular basis in response to treatment with buprenorphine or methadone, we favor second-line treatment with the alternative opioid agonist (ie, methadone or buprenorphine, respectively). For patients who initially received transmucosal buprenorphine, treatment with LAI buprenorphine is a reasonable alternative. (See "Pharmacotherapy for opioid use disorder", section on 'Opioid agonists'.)

- For patients with opioid use disorder who fail to stop using illicit opioids on a repeated and regular basis in response to treatment with methadone or buprenorphine, we favor third-line treatment with LAI naltrexone. Patients unable to tolerate the transition to naltrexone could be continued on an agonist combined with an intensification of psychosocial treatment. (See "Pharmacotherapy for opioid use disorder", section on 'Long-acting injectable naltrexone'.)

- For patients with opioid use disorder who prefer psychosocial treatment alone despite education and clinician recommendation of MAT, we generally start treatment with an evidence-based psychosocial intervention in conjunction with addiction counseling and participation in a mutual help group. If the patient is unable to stop using illicit opioids on a repeated and regular basis after 30 days of treatment, we would add an additional evidence-based intervention (eg, contingency management). Increase in the frequency of the interventions can be tried before an additional intervention is added. (See 'Psychosocial treatment alone' above.)

REFERENCES

1. Friedrichs A, Spies M, Härter M, Buchholz A. Patient Preferences and Shared Decision Making in the Treatment of Substance Use Disorders: A Systematic Review of the Literature. PLoS One 2016; 11:e0145817.
2. Friedmann PD, Hendrickson JC, Gerstein DR, Zhang Z. The effect of matching comprehensive services to patients' needs on drug use improvement in addiction treatment. Addiction 2004; 99:962.
3. Mattick RP, Breen C, Kimber J, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. Cochrane Database Syst Rev 2014; :CD002207.
4. Mattick RP, Breen C, Kimber J, Davoli M. Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. Cochrane Database Syst Rev 2009; :CD002209.
5. Minozzi S, Amato L, Vecchi S, et al. Oral naltrexone maintenance treatment for opioid dependence. Cochrane Database Syst Rev 2011; :CD001333.
6. Jones HE, Wong CJ, Tuten M, Stitzer ML. Reinforcement-based therapy: 12-month evaluation of an outpatient drug-free treatment for heroin abusers. Drug Alcohol Depend 2005; 79:119.
7. Tuten M, DeFulio A, Jones HE, Stitzer M. Abstinence-contingent recovery housing and reinforcement-based treatment following opioid detoxification. Addiction 2012; 107:973.
8. Petry NM, Carroll KM. Contingency management is efficacious in opioid-dependent outpatients not maintained on agonist pharmacotherapy. Psychol Addict Behav 2013; 27:1036.

9. Gunne LM, Grönbladh L. The Swedish methadone maintenance program: a controlled study. Drug Alcohol Depend 1981; 7:249.
10. Kakko J, Svanborg KD, Kreek MJ, Heilig M. 1-year retention and social function after buprenorphine-assisted relapse prevention treatment for heroin dependence in Sweden: a randomised, placebo-controlled trial. Lancet 2003; 361:662.
11. Lee JD, Nunes EV Jr, Novo P, et al. Comparative effectiveness of extended-release naltrexone versus buprenorphine-naloxone for opioid relapse prevention (X:BOT): a multicentre, open-label, randomised controlled trial. Lancet 2018; 391:309.
12. Tanum L, Solli KK, Latif ZE, et al. Effectiveness of Injectable Extended-Release Naltrexone vs Daily Buprenorphine-Naloxone for Opioid Dependence: A Randomized Clinical Noninferiority Trial. JAMA Psychiatry 2017; 74:1197.
13. Fischer G, Gombas W, Eder H, et al. Buprenorphine versus methadone maintenance for the treatment of opioid dependence. Addiction 1999; 94:1337.
14. Eder H, Fischer G, Gombas W, et al. Comparison of buprenorphine and methadone maintenance in opiate addicts. Eur Addict Res 1998; 4 Suppl 1:3.
15. Luty J, O'Gara C, Sessay M. Is methadone too dangerous for opiate addiction? BMJ 2005; 331:1352.
16. Bell JR, Butler B, Lawrance A, et al. Comparing overdose mortality associated with methadone and buprenorphine treatment. Drug Alcohol Depend 2009; 104:73.
17. Comer SD, Sullivan MA, Yu E, et al. Injectable, sustained-release naltrexone for the treatment of opioid dependence: a randomized, placebo-controlled trial. Arch Gen Psychiatry 2006; 63:210.
18. Krupitsky E, Nunes EV, Ling W, et al. Injectable extended-release naltrexone for opioid dependence: a double-blind, placebo-controlled, multicentre randomised trial. Lancet 2011; 377:1506.
19. Tiihonen J, Krupitsky E, Verbitskaya E, et al. Naltrexone implant for the treatment of polydrug dependence: a randomized controlled trial. Am J Psychiatry 2012; 169:531.
20. Sullivan M, Bisaga A, Pavlicova M, et al. Long-Acting Injectable Naltrexone Induction: A Randomized Trial of Outpatient Opioid Detoxification With Naltrexone Versus Buprenorphine. Am J Psychiatry 2017; 174:459.
21. Schwartz RP, Kelly SM, Mitchell SG, et al. Patient-centered methadone treatment: a randomized clinical trial. Addiction 2017; 112:454.
22. Davis DR, Kurti AN, Skelly JM, et al. A review of the literature on contingency management in the treatment of substance use disorders, 2009-2014. Prev Med 2016; 92:36.

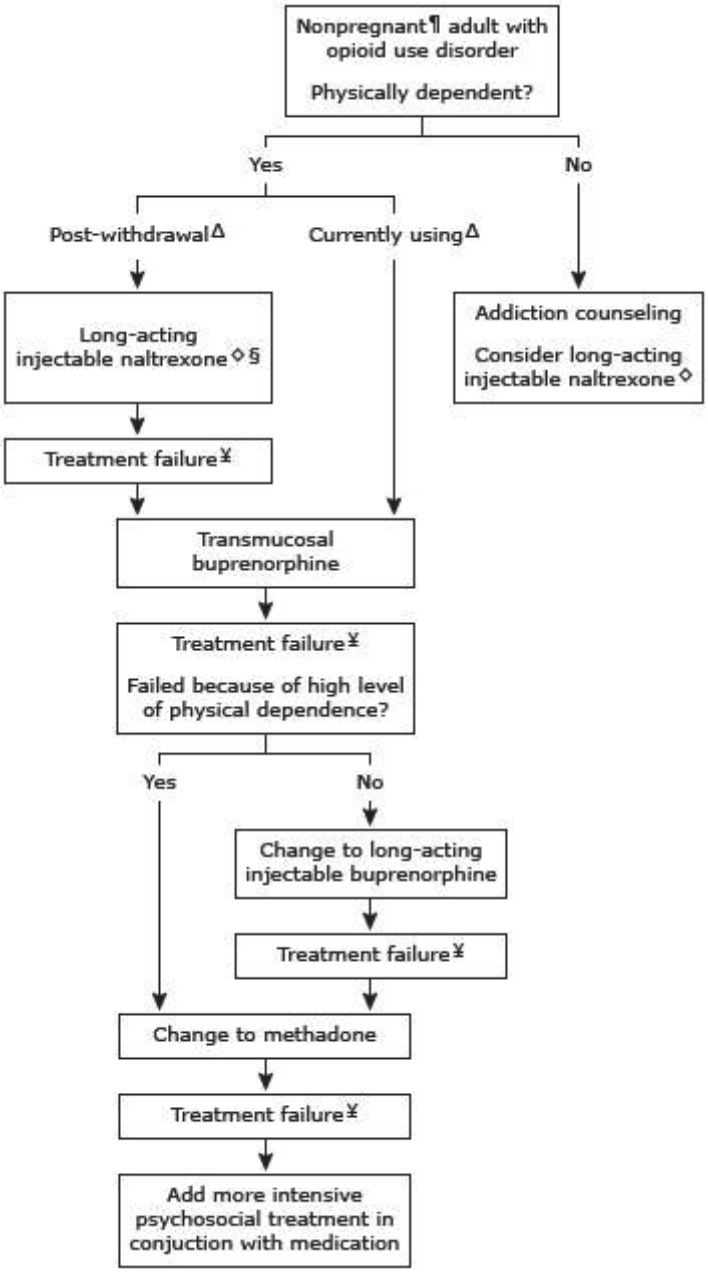
23. Dugosh K, Abraham A, Seymour B, et al. A Systematic Review on the Use of Psychosocial Interventions in Conjunction With Medications for the Treatment of Opioid Addiction. J Addict Med 2016; 10:93.
24. Schwartz RP, Kelly SM, O'Grady KE, et al. Randomized trial of standard methadone treatment compared to initiating methadone without counseling: 12-month findings. Addiction 2012; 107:943.
25. Calsyn DA, Wells EA, Saxon AJ, et al. Contingency management of urinalysis results and intensity of counseling services have an interactive impact on methadone maintenance treatment outcome. J Addict Dis 1994; 13:47.
26. Gruber VA, Delucchi KL, Kielstein A, Batki SL. A randomized trial of 6-month methadone maintenance with standard or minimal counseling versus 21-day methadone detoxification. Drug Alcohol Depend 2008; 94:199.
27. Saxon AJ, Wells EA, Fleming C, et al. Pre-treatment characteristics, program philosophy and level of ancillary services as predictors of methadone maintenance treatment outcome. Addiction 1996; 91:1197.
28. Fishman M, Wenzel K, Vo H, et al. A pilot randomized controlled trial of assertive treatment including family involvement and home delivery of medication for young adults with opioid use disorder. Addiction 2021; 116:548.
29. Weiss RD, Potter JS, Fiellin DA, et al. Adjunctive counseling during brief and extended buprenorphine-naloxone treatment for prescription opioid dependence: a 2-phase randomized controlled trial. Arch Gen Psychiatry 2011; 68:1238.
30. Smedslund G, Berg RC, Hammerstrøm KT, et al. Motivational interviewing for substance abuse. Cochrane Database Syst Rev 2011; :CD008063.
31. Sullivan MA, Bisaga A, Pavlicova M, et al. A Randomized Trial Comparing Extended-Release Injectable Suspension and Oral Naltrexone, Both Combined With Behavioral Therapy, for the Treatment of Opioid Use Disorder. Am J Psychiatry 2019; 176:129.
32. Hulse GK, Morris N, Arnold-Reed D, Tait RJ. Improving clinical outcomes in treating heroin dependence: randomized, controlled trial of oral or implant naltrexone. Arch Gen Psychiatry 2009; 66:1108.
33. Ling W, Casadonte P, Bigelow G, et al. Buprenorphine implants for treatment of opioid dependence: a randomized controlled trial. JAMA 2010; 304:1576.
34. Rosenthal RN, Ling W, Casadonte P, et al. Buprenorphine implants for treatment of opioid dependence: randomized comparison to placebo and sublingual buprenorphine/naloxone. Addiction 2013; 108:2141.

35. Rosenthal RN, Lofwall MR, Kim S, et al. Effect of Buprenorphine Implants on Illicit Opioid Use Among Abstinent Adults With Opioid Dependence Treated With Sublingual Buprenorphine: A Randomized Clinical Trial. JAMA 2016; 316:282.
36. Zedler BK, Mann AL, Kim MM, et al. Buprenorphine compared with methadone to treat pregnant women with opioid use disorder: a systematic review and meta-analysis of safety in the mother, fetus and child. Addiction 2016; 111:2115.
37. Auriacombe M, Franques P, Tignol J. Deaths attributable to methadone vs buprenorphine in France. JAMA 2001; 285:45.
38. Rodriguez CE, Klie KA. Pharmacological treatment of opioid use disorder in pregnancy. Semin Perinatol 2019; 43:141.
39. Kelty E, Hulse G. A Retrospective Cohort Study of Birth Outcomes in Neonates Exposed to Naltrexone in Utero: A Comparison with Methadone-, Buprenorphine- and Non-opioid-Exposed Neonates. Drugs 2017; 77:1211.
40. Kelty E, Hulse G. A Retrospective Cohort Study of Obstetric Outcomes in Opioid-Dependent Women Treated with Implant Naltrexone, Oral Methadone or Sublingual Buprenorphine, and Non-Dependent Controls. Drugs 2017; 77:1199.
41. Prochaska JO, DiClemente CC, Norcross JC. In search of how people change. Applications to addictive behaviors. Am Psychol 1992; 47:1102.
42. Donovan DM, Daley DC, Brigham GS, et al. Stimulant abuser groups to engage in 12-step: a multisite trial in the National Institute on Drug Abuse Clinical Trials Network. J Subst Abuse Treat 2013; 44:103.
43. Kakko J, Grönbladh L, Svanborg KD, et al. A stepped care strategy using buprenorphine and methadone versus conventional methadone maintenance in heroin dependence: a randomized controlled trial. Am J Psychiatry 2007; 164:797.

Topic 108803 Version 5.0

GRAPHICS

Approach to medication-assisted treatment for opioid use disorder*



Some patients who respond to medication-assisted treatment are satisfied to remain on the medication indefinitely. Patients who wish to discontinue the medication can receive a trial taper after months fully free from problematic substance use and related behaviors.

* Medication-assisted treatment includes integrated, adjunctive psychosocial treatment. We suggest beginning with addiction counseling and participation in a mutual help group. Inadequate response to medication may result in increases to the number and/or types of interventions.

¶ Opioid withdrawal and treatment with opioid antagonist should be avoided in pregnant women with opioid use disorder. The selection of medication to treat opioid use disorder during pregnancy is discussed in the topic on methadone substitution therapy for opioid use disorder during pregnancy.

Δ Completed withdrawal is needed prior to naltrexone but not prior to buprenorphine or

methadone. For some patients, however, the choice of medications is not made until after withdrawal has been completed. Initial agonist dosing after withdrawal should be adjusted accordingly, given the lower level of physical dependence in such cases.

◊ Supervised daily oral naltrexone is a reasonable alternative to long-acting injectable naltrexone in highly motivated patients who refuse injections or have good external support.

§ Naltrexone is generally suggested for highly motivated patients with mild opioid use disorder; however, for some patients with more severe opioid use disorder, naltrexone may be preferred by the patient or buprenorphine and methadone may be unavailable.

¥ Treatment failure as indicated by poor attendance and/or continual, ongoing illicit opioid use (eg, nearly every urine drug screen is positive for illicit opioids) at maximally tolerated dose. Too often an inadequate dose is used and treatment failure is then inaccurately claimed.

Graphic 115474 Version 2.0

Contributor Disclosures

Andrew J Saxon, MD Consultant/Advisory Boards: Alkermes Inc [Opioid use disorder]; Indivior [Opioid use disorder]. Other Financial Interest: Alkermes Inc [Opioid use disorder]. **Eric Strain, MD** Grant/Research/Clinical Trial Support: Masimo/Innovative Health Solutions [Opioid use disorder]. Consultant/Advisory Boards: Pinney Associates [Opioid use disorder]; The Oak Group [Opioid use disorder]; Caron [Opioid use disorder]; Crossroads Medical [Opioid use disorder]; Otsuka Pharmaceutical Development and Commercialization, Inc [Opioid use disorder]; Cerevel [Opioid use disorder]; Sophrosyne Pharmaceutics [Opioid use disorder]. **K Michelle Peavy, PhD, MAC** Nothing to disclose **Richard Saitz, MD, MPH, FACP, DFASAM** Grant/Research/Clinical Trial Support: Alkermes [Alkermes provides study medication for a clinical trial supported by NIH on alcohol use disorder]. Consultant/Advisory Boards: Checkup & Choices [Electronic interventions for alcohol use in primary care]. **Michael Friedman, MD** Nothing to disclose

Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

Conflict of interest policy

Buprenorphine: Drug information

(For additional information see "Buprenorphine: Patient drug information" and see "Buprenorphine: Pediatric drug information")

For abbreviations and symbols that may be used in Lexicomp (show table)

Special Alerts

REMS Drugs COVID-19 Safety Alert March 2020

Due to challenges with completion of required laboratory testing or imaging studies for REMS drugs because of self-isolation or quarantine during the COVID-19 public health emergency, the FDA is recommending health care providers prescribing and/or dispensing REMS drugs consider whether there are compelling reasons or not to complete these requirements during this public health emergency and weigh with the patient the benefits and risks of continuing treatment in the absence of the laboratory testing and imaging studies. The FDA will not take action against sponsors and others during the public health emergency for failing to adhere to REMS requirements.

Further information may be found at https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-provides-update-patient-access-certain-rems-drugs-during-covid-19.

ALERT: US Boxed Warning

Accidental exposure (buccal film, transdermal patch):

> Accidental exposure to even one dose of buprenorphine, especially by children, can result in a fatal overdose of buprenorphine.

Addiction, abuse, and misuse (buccal film, immediate-release injection, transdermal patch):

Buprenorphine exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing buprenorphine and monitor all patients regularly for the development of these behaviors or conditions.

Opioid analgesic risk evaluation and mitigation strategy (REMS):

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the FDA has required a REMS for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to health care providers. Health care providers are strongly encouraged to complete a REMS-compliant education program and counsel patients and/or their caregivers, with every prescription, on safe use, serious risks, storage, and disposal of these products; emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist, and consider other tools to improve patient, household, and community safety.

Life-threatening respiratory depression (buccal film, immediate-release injection, transdermal patch):

Serious, life-threatening, or fatal respiratory depression may occur with use of buprenorphine. Monitor for respiratory depression, especially during initiation of buprenorphine or following a dose increase. Misuse or abuse of buprenorphine by chewing, swallowing, snorting, or injecting buprenorphine extracted from the buccal film or transdermal system will result in the uncontrolled delivery of buprenorphine and pose a significant risk of overdose and death.

Neonatal opioid withdrawal syndrome (buccal film, immediate-release injection, transdermal patch):

Prolonged use of buprenorphine during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Risk associated with insertion and removal (subdermal implant):

Insertion and removal of buprenorphine implant are associated with the risk of implant migration, protrusion, and expulsion resulting from the procedure. Rare but serious

complications including nerve damage and migration resulting in embolism and death may result from improper insertion of drug implants inserted in the upper arm. Additional complications may include local migration, protrusion, and expulsion. Incomplete insertions or infections may lead to protrusion or expulsion.

Because of the risks associated with insertion and removal, buprenorphine implant is available only through a restricted program called the Probuphine REMS Program. All healthcare providers must successfully complete a live training program on the insertion and removal procedures and become certified, prior to performing insertions or prescribing buprenorphine implants. Patients must be monitored to ensure that the implant is removed by a healthcare provider certified to perform insertions.

Risks from concomitant use with benzodiazepines or other CNS depressants (buccal film, immediate-release injection, transdermal patch):

Concomitant use of opioids with benzodiazepines or other CNS depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing of buprenorphine and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients for signs and symptoms of respiratory depression and sedation.

Risk of serious harm or death with intravenous administration (extended-release injection):

Serious harm or death could result if extended-release injection is administered intravenously. The injection forms a solid mass upon contact with body fluids and may cause occlusion, local tissue damage, and thromboembolic events, including life-threatening pulmonary emboli if administered intravenously.

Because of the risk of serious harm or death that could result from intravenous self-administration, buprenorphine extended-release injection is only available through a restricted program called the Sublocade REMS Program. Healthcare settings and pharmacies that order and dispense buprenorphine extended-release injection must be certified in this program and comply with the REMS requirements.

Brand Names: US

Belbuca; Buprenex; Butrans; Probuphine Implant Kit; Sublocade

Brand Names: Canada

Belbuca [DSC]; BuTrans 10; BuTrans 15; BuTrans 20; BuTrans 5; Probuphine; Sublocade; Subutex

Pharmacologic Category

Analgesic, Opioid; Analgesic, Opioid Partial Agonist

Dosing: Adult

Note: Buprenorphine 8 mg sublingual tablet = buprenorphine/naloxone 8 mg/2 mg sublingual film = buprenorphine/naloxone 4.2 mg/0.7 mg buccal film = buprenorphine/naloxone 5.7 mg/1.4 mg sublingual tablet.

Acute pain (moderate to severe): Note: Long-term use is not recommended. The following recommendations are guidelines and do not represent the maximum doses that may be required in all patients. Doses should be titrated to pain relief/prevention.

IR injection:

IM: Initial: 0.3 mg every 6 to 8 hours as needed; initial dose (up to 0.3 mg) may be repeated once in 30 to 60 minutes after the initial dose if needed.

Slow IV: Initial: 0.3 mg every 6 to 8 hours as needed; initial dose (up to 0.3 mg) may be repeated once in 30 to 60 minutes after the initial dose if needed.

Chronic pain (moderate to severe):

Buccal film: Note: Buprenorphine buccal film doses of 600, 750, and 900 mcg are only for use following titration from lower doses (maximum dose: 900 mcg every 12 hours).

Opioid-naive patients and opioid-non-tolerant patients: Initial: 75 mcg once daily or, if tolerated, every 12 hours for ≥4 days, then increase to 150 mcg every 12 hours.

Opioid-experienced patients (conversion from other opioids to buprenorphine): Discontinue all other around-the-clock opioids when buprenorphine is initiated. Taper patient's current opioid to no more than 30 mg oral morphine sulfate equivalents daily before initiating buprenorphine. Following analgesic taper, base the initial buprenorphine dose on the patient's daily opioid dose prior to taper. Patients may require additional short-acting analgesics during the taper period.

Patients who were receiving daily dose of <30 mg of oral morphine equivalents: Initial: 75 mcg once daily or every 12 hours.

Patients who were receiving daily dose of 30 to 89 mg of oral morphine equivalents: Initial: 150 mcg every 12 hours.

Patients who were receiving daily dose of 90 to 160 mg of oral morphine equivalents: Initial: 300 mcg every 12 hours.

Patients who were receiving daily dose of >160 mg of oral morphine equivalents: Buprenorphine buccal film may not provide adequate analgesia; **consider the use of an alternate analgesic.**

Conversion from methadone: Close monitoring is required when converting methadone to another opioid. Ratio between methadone and other opioid agonists varies widely according to previous dose exposure. Methadone has a long half-life and can accumulate in the plasma.

Dose titration (opioid-naive or opioid-experienced patients): Individually titrate in increments of 150 mcg every 12 hours, no more frequently than every 4 days, to a dose that provides adequate analgesia and minimizes adverse reactions (maximum dose: 900 mcg every 12 hours; doses up to 450 mcg every 12 hours were studied in opioid naive patients). Patients may require additional short-acting analgesics during titration.

Discontinuation of therapy: When discontinuing buccal film, use a gradual downward titration, such as decreasing the dose by no more than 10% to 25% in a physically dependent patient and continue downward titration every 2 to 4 weeks. If patient displays withdrawal symptoms, temporarily interrupt the taper or increase dose to previous level and then reduce dose more slowly by increasing interval between dose reductions, decreasing amount of daily dose reduction, or both.

Patients with oral mucositis: Reduce the starting dose and titration incremental dose by 50%.

Transdermal patch:

Opioid-naive patients: Initial: 5 **mcg**/hour applied once every 7 days.

Opioid-experienced patients (conversion from other opioids to buprenorphine): Discontinue all other around-the-clock opioid drugs when buprenorphine therapy is initiated. Short-acting analgesics as needed may be continued until analgesia

with transdermal buprenorphine is attained. There is a potential for buprenorphine to precipitate withdrawal in patients already receiving opioids.

Patients who were receiving daily dose of <30 mg of oral morphine equivalents: Initial: 5 **mcg**/hour applied once every 7 days.

Patients who were receiving daily dose of 30 to 80 mg of oral morphine equivalents: Taper the current around-the-clock opioid for up to 7 days to ≤30 mg/day of oral morphine or equivalent before initiating therapy. Initial: 10 **mcg**/hour applied once every 7 days.

Patients who were receiving daily dose of >80 mg of oral morphine equivalents: Buprenorphine transdermal patch, even at the maximum dose of 20 **mcg**/hour applied once every 7 days, may not provide adequate analgesia; **consider the use of an alternate analgesic.**

Dose titration (opioid-naive or opioid-experienced patients): May increase dose in 5 mcg/hour, 7.5 mcg/hour, or 10 mcg/hour increments (using no more than two patches), based on patient's supplemental short-acting analgesic requirements, with a minimum titration interval of 72 hours (maximum dose: 20 mcg/hour applied once every 7 days; risk for QTc prolongation increases with doses >20 mcg/hour patch).

Discontinuation of therapy: When discontinuing transdermal patch, use a gradual downward titration, such as decreasing the dose by no more than 10% to 25% in a physically dependent patient and continue downward titration every 2 to 4 weeks. If patient displays withdrawal symptoms, temporarily interrupt the taper or increase dose to previous level and then reduce dose more slowly by increasing interval between dose reductions, decreasing amount of daily dose reduction, or both.

Opioid use disorder: Note: Prior to induction, consider type of opioid use (ie, long- or short-acting opioid) and time since last use of opioid. Patients on heroin or short-acting opioids should initiate buprenorphine when signs of opioid withdrawal occur, but no sooner than 12 hours after the last opioid use (ASAM 2020; SAMHSA 2018). See dosing section below on “Switching therapies” for guidance on transitioning from methadone to buprenorphine.

ER injection: SUBQ: Initial: 300 mg monthly for the first 2 months, after treatment has been inducted and adjusted with 8 to 24 mg of a transmucosal buprenorphine-

containing product for a minimum of 7 days. Maintenance: 100 mg monthly, increasing to 300 mg monthly for patients who tolerate the 100 mg dose but do not demonstrate a satisfactory clinical response (as evidenced by self-reported illicit opioid use or urine drug screens positive for illicit opioid use). **Note**: Administer doses ≥26 days apart.

Missed dose: Administer a missed dose as soon as possible, with the following dose given no less than 26 days later; dosing delays of up to 2 weeks are not expected to impact treatment.

Extended interval dosing (only for use in select instances such as extended travel): Patients established on a maintenance dose of 100 mg monthly may receive a single 300 mg dose to cover a 2-month period followed by resumption of the 100 mg monthly dose. Patients should be cautioned about sedation and other buprenorphine-related effects due to higher peak levels following the 300 mg dose.

Transition from long-term buprenorphine transmucosal treatment: Patients established on long-term transmucosal buprenorphine 8 to 24 mg treatment and whose disease symptoms are controlled may be directly transitioned to the ER injection:

Transmucosal buprenorphine 8 to 18 mg: Initial: 300 mg, followed by 100 mg for the second dose; may consider 300 mg for second injection in patients still experiencing craving or withdrawal symptoms after initial 300 mg dose. Maintenance: 100 mg monthly.

Transmucosal buprenorphine 20 to 24 mg: Initial: 300 mg monthly for first 2 months. Maintenance: 100 mg monthly.

Subdermal implant: Insert 4 implants subdermally in the inner side of the upper arm 12 to 24 hours after last dose of transmucosal buprenorphine-containing product (SAMHSA 2018). Remove no later than 6 months after the date of insertion; if continued treatment is desired, insert 4 new implants subdermally in the inner side of the contralateral arm. After one insertion in each arm, discontinue treatment with subdermal implants.

Converting back to sublingual tablet: On day of implant removal, resume buprenorphine treatment at previous sublingual dose.

Sublingual tablet:

Initial: 2 to 4 mg; consider an initial dose of 1 mg in patients with a history of opioid use disorder with a high risk of relapse but not currently dependent on opioids; titration in these patients should occur much more slowly than tolerant patients to avoid oversedation/overdose. If no signs of precipitated withdrawal after 60 to 90 minutes and dose is tolerated, may increase dose in increments of 2 to 4 mg to a dose that is clinically effective and provides 24 hours of stabilization (ASAM 2020; SAMHSA 2018).

Maintenance: After the first day of treatment, maintain total daily dose from day 1 and adjust dose in increments of 4 mg to a level that maintains treatment and suppresses opioid withdrawal symptoms. Doses ≥16 mg/day have been associated with greater efficacy; limited evidence exists for doses >24 mg/day. In patients with pain, temporarily increasing the dose by 20% to 25% or dosing frequency (eg, divide total daily dose over 3 to 4 times per day) may maximize the analgesic properties for pain management (ASAM 2020; Strain 2021).

Discontinuation of therapy: When discontinuing sublingual buprenorphine for long-term treatment of opioid use disorder, use a gradual downward titration of the dose over several months to prevent withdrawal; do not abruptly discontinue (ASAM 2020; SAMHSA 2018).

Switching therapies:

Buprenorphine to methadone: No time delay is required (ASAM 2020).

Methadone to buprenorphine: Taper the methadone dose gradually to 30 to 40 mg per day and remain on that dose for ≥7 days. The patient should be in mild withdrawal before starting buprenorphine; this is typically 24 to 48 hours after the last dose of methadone. Initiating buprenorphine at lower doses (eg, 2 mg) decreases risk of precipitated methadone withdrawal (ASAM 2020, SAMHSA 2018).

Buprenorphine to naltrexone: Taper the buprenorphine dose gradually and discontinue. Wait 7 to 14 days before initiating treatment with naltrexone. A naloxone challenge may be used to demonstrate an absence of physical dependence (ASAM 2020).

Opioid withdrawal in heroin-dependent hospitalized patients (off-label use): IR injection: IV infusion: 0.3 to 0.9 mg (diluted in 50 to 100 mL of NS) over 20 to 30 minutes every 6 to 12 hours (Welsh 2002).

Perineural anesthesia (off-label use): IR perineural injection: 200 to 300 mcg added to local anesthetic (eg, bupivacaine, mepivacaine, tetracaine) with or without epinephrine and administered as a single injection (Kosel 2015; Krishnan 2016).

Dosage adjustment for concomitant therapy: Significant drug interactions exist, requiring dose/frequency adjustment or avoidance. Consult drug interactions database for more information.

Dosing: Renal Impairment: Adult

There are no dosage adjustments provided in the manufacturer's labeling (has not been adequately studied); use with caution. In pharmacokinetic studies, renal impairment (including administration pre- or post-hemodialysis) was not associated with increased buprenorphine plasma concentrations.

Dosing: Hepatic Impairment: Adult

Buccal film:

Mild impairment (Child-Pugh class A): No dosage adjustment necessary.

Moderate impairment (Child-Pugh class B): No dosage adjustment necessary; use caution and monitor for signs and symptoms of toxicity or overdose.

Severe impairment (Child-Pugh class C): Reduce starting dose and reduce titration dose by 50% (ie, from 150 mcg to 75 mcg).

ER injection (SUBQ):

Mild impairment: There are no dosage adjustments provided in the manufacturer's labeling.

Moderate to severe impairment: Use is not recommended. If signs and symptoms of hepatic impairment occur within 2 weeks of injection, removal of depot may be required. Monitor for signs and symptoms of toxicity or overdose.

IR injection (IM, IV):

Mild or moderate impairment: There are no dosage adjustments provided in the manufacturer's labeling; however, need for dosage adjustment is unlikely as systemic exposure following IV buprenorphine in these patients was similar to healthy subjects.

Severe impairment: There are no dosage adjustments provided in the manufacturer's labeling; use with caution.

Subdermal implant:

Mild impairment: There are no dosage adjustments provided in the manufacturer's labeling (has not been studied).

Moderate or severe impairment: Use is not recommended.

Sublingual:

Mild impairment: No dosage adjustment necessary.

Moderate impairment: No dosage adjustment necessary; use caution and monitor for signs and symptoms of toxicity or overdose.

Severe impairment: Consider reducing initial and titration incremental dose by 50%; monitor for signs and symptoms of toxicity or overdose.

Transdermal patch:

Mild or moderate impairment: There are no dosage adjustments provided in the manufacturer's labeling; however, need for dosage adjustment is unlikely as systemic exposure following IV buprenorphine in these patients was similar to that observed in healthy subjects.

Severe impairment: There are no dosage adjustments provided in the manufacturer's labeling (has not been studied); consider alternative therapy with more flexibility for dosing adjustments.

Dosing: Pediatric

(For additional information see "Buprenorphine: Pediatric drug information")

Acute pain (moderate to severe): Dose should be titrated to appropriate effect. The following recommendations are guidelines and do not represent the maximum doses that may be required in all patients.

Children 2 to 12 years: IM, slow IV injection: Initial: Opioid-naive: 2 to 6 **mcg**/kg/dose every 4 to 6 hours (APS 2016); **Note:** Not all children have faster clearance rates than adults; some children may require dosing intervals of every 6 to 8 hours; observe clinical effects to establish the proper dosing interval.

Adolescents: IM, slow IV injection: Initial: Opioid-naive: 0.3 mg every 6 to 8 hours as needed; initial dose may be repeated once in 30 to 60 minutes if clinically needed

Chronic pain (moderate to severe): Adolescents ≥18 years: Transdermal patch:

Opioid-naive patients*:* Initial: 5 **mcg**/hour applied once every 7 days

Opioid-experienced patients (conversion from other opioids to buprenorphine patch): Discontinue all other around-the-clock opioid drugs when buprenorphine therapy is initiated. Short-acting analgesics as needed may be continued until analgesia with transdermal buprenorphine is attained. There is a potential for buprenorphine to precipitate withdrawal in patients already receiving opioids.

Patients who were receiving daily dose of <30 mg of oral morphine equivalents: Initial: 5 **mcg**/hour applied once every 7 days

Patients who were receiving daily dose of 30 to 80 mg of oral morphine equivalents: Taper the current around-the-clock opioid for up to 7 days to ≤30 mg/day of oral morphine or equivalent before initiating therapy. Initial: 10 **mcg**/hour applied once every 7 days.

Patients who were receiving daily dose of >80 mg of oral morphine equivalents: Buprenorphine transdermal patch, even at the maximum dose of 20 **mcg**/hour applied once every 7 days, may not provide adequate analgesia; consider the use of an alternate analgesic.

Dose titration (opioid-naive or opioid-experienced patients): May increase dose in 5 **mcg**/hour, 7.5 **mcg**/hour, or 10 **mcg**/hour increments (using no more than two 5 **mcg**/hour patches); titrate no more frequently than every 72 hours; maximum dose: 20 **mcg**/hour applied once every 7 days due to risk of QTc prolongation associated with higher doses.

Discontinuation of therapy: Taper dose gradually every 7 days to prevent withdrawal in the physically dependent patient; consider initiating immediate-release opioids, if needed for signs and symptoms of withdrawal.

Opioid dependence: Note: Do not start induction with buprenorphine until objective and clear signs of withdrawal are apparent (otherwise withdrawal may be precipitated).

Sublingual tablet: **Note**: The combination product, buprenorphine and naloxone, is preferred therapy over buprenorphine monotherapy for induction treatment (and

stabilization/maintenance treatment) for short-acting opioid dependence (US Department of Health and Human Services 2005)

American Society of Addiction Medicine Guidelines (Kampman [ASAM 2015]): Limited data available: Adolescents: Sublingual tablet:

Note: Buprenorphine treatment initiation should begin after mild to moderate opioid withdrawal signs appear (to avoid precipitated withdrawal), which is generally at least 6 to 12 hours after last use of short-acting opioids (eg, heroin, oxycodone) and 24 to 72 hours after last use of long-acting opioids (methadone).

Induction: Initial: 2 to 4 mg; if no signs of precipitated withdrawal after 60 to 90 minutes, may increase in increments of 2 to 4 mg. Once initial dose is tolerated, may increase to a dose that is clinically effective and provides 24 hours of stabilization.

After induction and titration, daily dose usually ≥8 mg/day are necessary. In patients continuing to use opioids, consider increasing the dose by 4 to 8 mg to a daily dose of ≥12 to 16 mg/day. Maximum daily dose 24 mg/**day.**

Manufacturer's labeling: Adolescents ≥16 years:

Induction: Day 1: 8 mg/day divided in 2 to 4 mg increments; day 2 and subsequent induction days dose dependent upon patient response. In 1 study, patients received 8 mg on day 1, followed by 16 mg on day 2; induction usually accomplished over 3 to 4 days. Treatment should begin only when objective and clear signs of moderate opioid withdrawal appear, and not less than 4 hours after last use of heroin or other short-acting opioids or not less than 24 hours after last use of methadone or other long-acting opioids. Titrating dose to clinical effectiveness should be done as rapidly as possible to prevent undue withdrawal symptoms and patient drop-out during the induction period.

Maintenance: Target dose: 16 mg/day; reported range: 4 to 24 mg/day; doses higher than 24 mg/day have not been demonstrated to provide any clinical advantage; patients should be switched to the buprenorphine/naloxone combination product for maintenance and unsupervised therapy

Subdermal implant: Adolescents ≥16 years: Insert 4 implants subdermally in the inner side of the upper arm. Remove no later than 6 months after the date of insertion; if continued treatment is desired, insert 4 new implants subdermally in the inner side of

the contralateral arm. After 1 insertion in each arm, discontinue treatment with subdermal implants.

To convert back to sublingual tablet: On day of implant removal, resume buprenorphine treatment at previous sublingual dose

Dosage adjustment for concomitant therapy: Significant drug interactions exist, requiring dose/frequency adjustment or avoidance. Consult drug interactions database for more information.

Dosing: Renal Impairment: Pediatric

There are no dosage adjustments provided in manufacturer's labeling (has not been studied); use with caution. In pharmacokinetic studies, renal impairment (including administration pre- or posthemodialysis) was not associated with increased buprenorphine plasma concentrations.

Dosing: Hepatic Impairment: Pediatric

Injection (immediate release): Children ≥2 years and Adolescents: Use caution due to extensive hepatic metabolism; dosage adjustments may be necessary.

Subdermal implant: Adolescents ≥16 years:

Mild impairment: There are no dosage adjustments provided in the manufacturer's labeling (has not been studied).

Moderate or severe impairment: Use is not recommended.

Dosing: Geriatric

Acute pain (moderate to severe): Immediate-release injection: IM, slow IV: Refer to adult dosing; use with caution.

Chronic pain (moderate to severe): Buccal film, transdermal patch: No specific dosage adjustments required; use caution and titrate slowly due to potential for increased risk of adverse events.

Opioid use disorder: Extended-release injection, subdermal implant: No specific dosage adjustments required; use caution due to potential for increased risk of adverse events and inability to adjust dosage.

Dosage Forms: US

Excipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Film, Buccal:

Belbuca: 75 mcg (60 ea [DSC]) [contains methylparaben, propylparaben, saccharin sodium, sodium benzoate]

Belbuca: 75 mcg (1 ea, 60 ea) [contains methylparaben, propylparaben, saccharin sodium, sodium benzoate; peppermint flavor]

Belbuca: 150 mcg (60 ea [DSC]) [contains methylparaben, propylparaben, saccharin sodium, sodium benzoate]

Belbuca: 150 mcg (1 ea, 60 ea) [contains methylparaben, propylparaben, saccharin sodium, sodium benzoate; peppermint flavor]

Belbuca: 300 mcg (60 ea [DSC]) [contains methylparaben, propylparaben, saccharin sodium, sodium benzoate]

Belbuca: 300 mcg (1 ea, 60 ea) [contains methylparaben, propylparaben, saccharin sodium, sodium benzoate; peppermint flavor]

Belbuca: 450 mcg (60 ea [DSC]) [contains methylparaben, propylparaben, saccharin sodium, sodium benzoate]

Belbuca: 450 mcg (1 ea, 60 ea) [contains methylparaben, propylparaben, saccharin sodium, sodium benzoate; peppermint flavor]

Belbuca: 600 mcg (60 ea [DSC]) [contains methylparaben, propylparaben, saccharin sodium, sodium benzoate]

Belbuca: 600 mcg (1 ea, 60 ea) [contains methylparaben, propylparaben, saccharin sodium, sodium benzoate; peppermint flavor]

Belbuca: 750 mcg (60 ea [DSC]) [contains methylparaben, propylparaben, saccharin sodium, sodium benzoate]

Belbuca: 750 mcg (1 ea, 60 ea); 900 mcg (1 ea, 60 ea) [contains methylparaben, propylparaben, saccharin sodium, sodium benzoate; peppermint flavor]

Implant, Subcutaneous:

Probuphine Implant Kit: 74.2 mg (4 ea)

Patch Weekly, Transdermal:

Butrans: 5 mcg/hr (4 ea); 7.5 mcg/hr (4 ea); 10 mcg/hr (4 ea); 15 mcg/hr (4 ea); 20 mcg/hr (4 ea)

Generic: 5 mcg/hr (1 ea, 4 ea); 7.5 mcg/hr (4 ea); 10 mcg/hr (1 ea, 4 ea); 15 mcg/hr (1 ea, 4 ea); 20 mcg/hr (1 ea, 4 ea)

Solution, Injection:

Buprenex: 0.3 mg/mL (1 mL)

Generic: 0.3 mg/mL (1 mL)

Solution, Injection [preservative free]:

Generic: 0.3 mg/mL (1 mL)

Solution Prefilled Syringe, Subcutaneous [preservative free]:

Sublocade: 100 mg/0.5 mL (0.5 mL); 300 mg/1.5 mL (1.5 mL)

Tablet Sublingual, Sublingual:

Generic: 2 mg, 8 mg

Generic Equivalent Available: US

May be product dependent

Dosage Forms Considerations

Note: Subdermal implant and subcutaneous implant both refer to Probuphine.

Dosage Forms: Canada

Excipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Film, Buccal:

Belbuca: 75 mcg ([DSC]); 150 mcg ([DSC]); 300 mcg ([DSC]); 450 mcg ([DSC]) [contains methylparaben, propylparaben, saccharin sodium, sodium benzoate]

Implant, Subcutaneous:

Probuphine: 74.2 mg (4 ea)

Patch Weekly, Transdermal:

BuTrans 5: 5 mcg/hr (4 ea)

BuTrans 10: 10 mcg/hr (4 ea)

BuTrans 15: 15 mcg/hr (4 ea)

BuTrans 20: 20 mcg/hr (4 ea)

Solution Prefilled Syringe, Subcutaneous:

Sublocade: 100 mg/0.5 mL (0.5 mL); 300 mg/1.5 mL (1.5 mL)

Tablet Sublingual, Sublingual:

Subutex: 2 mg, 8 mg

Controlled Substance

C-III

Prescribing and Access Restrictions

Extended-release injection: Prescribing of the extended release injection is limited to healthcare providers who meet qualifying requirements, have notified the Secretary of Health and Human Services (HHS) of their intent to prescribe this product for the treatment of opioid dependence and have been assigned a unique identification number to include on every prescription.

Subdermal implant: Prescribing of implants and inserting or removing implants are limited to healthcare providers who have completed a live training program. Additionally, inserting or removing implants is limited to healthcare providers who have demonstrated procedural competency. As a prerequisite for participating in the live training program, the healthcare provider must have performed at least one qualifying surgical procedure in the last 3 months. Qualifying procedures are those performed under local anesthesia using aseptic technique and include, at a minimum, making skin incisions or placing sutures. Buprenorphine subdermal implant will only be distributed to certified prescribers through a restricted distribution program. Information concerning the insertion and removal procedures can be obtained by calling 1-844-859-6341.

Sublingual tablet: Prescribing of tablets for opioid dependence is limited to physicians who have met the qualification criteria and have received a DEA number specific to prescribing

this product. Tablets will be available through pharmacies and wholesalers which normally provide controlled substances.

Medication Guide and/or Vaccine Information Statement (VIS)

An FDA-approved patient medication guide, which is available with the product information and as follows, must be dispensed with this medication:

Belbuca:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/207932s015lbl.pdf#page=37

Butrans:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/021306s037lbl.pdf#page=43

Probuphine implant:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/204442s009lbl.pdf#page=49

Sublocade:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/209819s018lbl.pdf#page=45

Subutex:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/020732s024lbl.pdf#page=29

Administration: Adult

IM: Administer IR injection via deep IM injection.

IV: Administer IR injection slowly, over at least 2 minutes. Administration over 20 to 30 minutes preferred when managing opioid withdrawal in heroin-dependent hospitalized patients (Welsh 2002).

Oral:

Buccal film: Prior to placing the film, moisten inside of cheek with tongue or water. Apply film with a dry finger immediately after removing it from packaging. Place yellow side of film against the inside of the moistened cheek; press and hold the film in place for 5 seconds with finger (film should stay in place after this period). Keep film in place until it dissolves completely (usually within 30 minutes of application). Do not chew,

swallow, touch, or move film after placement. Avoid eating or drinking until film dissolves. Do not cut or tear the film. Avoid application to areas of the mouth with any open sores or lesions. To dispose of film; remove foil overwrap from any unused, unneeded films and dispose by flushing down the toilet.

Sublingual tablet: Tablet should be placed under the tongue until dissolved (can take up to 10 minutes to fully dissolve [SAMHSA 2018]); should not be chewed or swallowed (swallowing tablets before dissolved reduces bioavailability). If two or more tablets are needed per dose, all may be placed under the tongue at once, or two at a time. To ensure consistent bioavailability, subsequent doses should always be taken the same way.

SUBQ injection: Administer ER injection as an abdominal SUBQ injection only, using only the syringe and safety needle included with product. Do not administer IV, IM, or intradermally. Inject between the transpyloric and transtubercular planes in an area with adequate SUBQ tissue that is free of skin conditions (eg, nodules, lesions, excessive pigment). Rotate the injection site between injections. Subsequent precipitation following injection results in a solid depot which will gradually release buprenorphine. The patient may have a lump for several weeks that will decrease over time; advise not to rub or massage the injection site. Wipe any blood or fluid at injection site with a cotton ball or gauze prior to applying a gauze pad or bandage (use minimal pressure when applying). In the event the depot from an ER injection must be removed, it can be surgically excised under local anesthesia within 14 days of injection. See prescribing information for details. For insertion by health care providers trained in the injection technique and certified through the REMS program.

Subdermal implant: For insertion under local anesthesia by health care providers trained in the insertion and removal procedure through the REMS program. See prescribing information for details.

Transdermal patch: Apply patch to intact, nonirritated skin only. Apply to a hairless or nearly hairless skin site. If hairless site is not available, do not shave skin; hair at application site should be clipped. Prior to application, if the site must be cleaned, clean with clear water and allow to dry completely; do not use soaps, alcohol, oils, lotions, or abrasives due to potential for increased skin absorption. Do not use any patch that has been damaged, cut or manipulated in any way. Remove patch from protective pouch immediately before application. Remove the protective backing and apply the sticky side of the patch to one of eight possible application sites (upper outer arm, upper chest, upper back or the side of the chest [each site on either side of the body]). Up to 2 patches may be applied at the same

time adjacent to one another at the same application site. Firmly press patch in place and hold for ~15 seconds. Change patch every 7 days. Rotate patch application sites whenever a patch is replaced or added; wait ≥21 days before reapplying another patch to the same skin site. Avoid exposing application site to external heat sources (eg, heating pad, electric blanket, heat lamp, hot tub). Incidental exposure to water while bathing or showering is acceptable based on experience during clinical studies. If there is difficulty with patch adhesion, the edges of the system may be taped in place with first-aid tape. If ineffective, the system may be covered with waterproof or semipermeable adhesive dressings suitable for 7 days of wear. If the patch falls off during the 7-day dosing interval, dispose of the patch and apply a new patch to a different skin site. Dispose of patches using the Patch-Disposal Unit or by folding the adhesive sides of the patch together and then flushing down the toilet. In Canada, disposal via a pharmacy take back program is recommended; trash disposal is not advised.

Administration: Pediatric

Oral:

Sublingual solution: Neonates: Place dose under tongue; insert pacifier to help reduce swallowing of dose (Kraft 2008; Kraft 2011; Kraft 2017)

Sublingual tablet: Adolescents ≥16 years: Place tablet under the tongue until dissolved; do not chew or swallow (swallowing tablets before dissolved reduces bioavailability). If 2 or more tablets are needed per dose, all tablets may be placed under the tongue at once, or 2 tablets may be placed under the tongue at a time; to ensure consistent bioavailability, subsequent doses should always be taken the same way.

Parenteral:

Immediate-release injection: Children ≥2 years and Adolescents:

IM: Administer via deep IM injection

IV: Administer slowly, over at least 2 minutes

Subdermal/Topical:

Subdermal implant: Adolescents ≥16 years: For insertion under local anesthesia by health care providers trained in the insertion and removal procedure through the REMS program. See prescribing information for details.

Transdermal patch: Adolescents ≥18 years: Apply patch to intact, nonirritated skin only. Apply to a hairless or nearly hairless skin site. If hairless site is not available, do not shave skin (as absorption from patch can be increased); hair at application site should be clipped. Prior to application, if the site must be cleaned, clean with clear water and allow to dry completely; do not use soaps, alcohol, lotions, or abrasives due to potential for increased skin absorption. Do not use any patch that has been damaged, cut, or manipulated in any way. Remove patch from protective pouch immediately before application. Remove the protective backing and apply the sticky side of the patch to 1 of 8 possible application sites (upper outer arm, upper chest, upper back, or the side of the chest [each site on either side of the body]). Up to 2 patches may be applied at the same time adjacent to one another at the same application site. Firmly press patch in place and hold for ~15 seconds. Change patch every 7 days. Rotate patch application sites whenever a patch is replaced or added; wait ≥21 days before reapplying another patch to the same skin site. Avoid exposing application site to external heat sources (eg, heating pad, electric blanket, heat lamp, hot tub). Incidental exposure to water while bathing or showering is acceptable based on experience during clinical studies. If there is difficulty with patch adhesion, the edges of the system may be taped in place with first-aid tape. If the patch falls off during the 7-day dosing interval, dispose of the patch and apply a new patch to a different skin site. Dispose of patches using the Patch-Disposal Unit or by folding the adhesive sides of the patch together and then flushing down the toilet.

Use: Labeled Indications

Opioid use disorder:

Extended-release injection: Maintenance treatment of moderate to severe opioid use disorder in patients who have initiated treatment with 8 to 24 mg of a transmucosal buprenorphine-containing product, followed by dose adjustment for a minimum of 7 days.

Subdermal implant: Maintenance treatment of opioid use disorder in patients who have achieved and sustained prolonged clinical stability on low to moderate doses (≤8 mg/day) of a transmucosal buprenorphine-containing product for 3 months or longer with no need for supplemental dosing or adjustments

Sublingual tablet: Medically supervised withdrawal and maintenance treatment of opioid use disorder.

Limitations of use: Buprenorphine should be used as part of a complete treatment program to include counseling and psychosocial support.

Pain management:

Buccal film, transdermal patch: Management of pain severe enough to require around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate

Immediate-release injection: Management of pain severe enough to require an opioid analgesic and for which treatments are inadequate

Limitations of use: Reserve buprenorphine for use in patients for whom alternative treatment options (eg, nonopioid analgesics, opioid combination products, immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain. Buprenorphine buccal film and transdermal patch are not indicated as an as needed analgesic.

Use: Off-Label: Adult

Opioid withdrawal in heroin-dependent hospitalized patients (immediate-release injection); Perineural anesthesia

Medication Safety Issues

Sound-alike/look-alike issues:

Buprenex may be confused with Brevibloc, Bumex

Buprenorphine may be confused with HYDROmorphone

High alert medication:

The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Adverse Reactions

The following adverse drug reactions and incidences are derived from product labeling unless otherwise specified. ER = extended-release.

Buccal film:

1% to 10%:

Cardiovascular: Hypertension (1% to <5%), peripheral edema (1% to <5%)

Dermatologic: Hyperhidrosis (1% to <5%), pruritus (1% to <5%), skin rash (1% to <5%)

Endocrine & metabolic: Hot flash (1% to <5%)

Gastrointestinal: Abdominal pain (1% to <5%), constipation (3% to ≥5%), decreased appetite (1% to <5%), diarrhea (≥5%), gastroenteritis (1% to <5%), nausea (9% to 10%), vomiting (4% to ≥5%), xerostomia (≥5%)

Genitourinary: Urinary tract infection (1% to <5%)

Hematologic & oncologic: Anemia (1% to <5%), bruise (1% to <5%)

Nervous system: Anxiety (1% to <5%), depression (1% to <5%), dizziness (2% to ≥5%), drowsiness (1% to ≥5%), falling (1% to <5%), fatigue (≥5%), headache (4% to ≥5%), insomnia (1% to <5%), opioid withdrawal syndrome (1% to <5%)

Neuromuscular & skeletal: Back pain (1% to <5%), muscle spasm (1% to <5%)

Respiratory: Bronchitis (1% to <5%), nasopharyngitis (1% to <5%), oropharyngeal pain (1% to <5%), paranasal sinus congestion (1% to <5%), sinusitis (1% to <5%), upper respiratory tract infection (≥5%)

Miscellaneous: Fever (1% to <5%)

<1%:

Cardiovascular: Atrial fibrillation, cerebrovascular accident, chest pain, coronary artery disease, prolonged QT interval on ECG, transient ischemic attacks, syncope

Dermatologic: Cellulitis, excoriation of skin

Endocrine & metabolic: Decreased plasma testosterone, dehydration

Gastrointestinal: Abdominal distress, cholecystitis, dyspepsia, intestinal obstruction, toothache

Hepatic: Abnormal hepatic function tests, increased serum aspartate aminotransferase

Infection: Tooth abscess

Nervous system: Chills, hypoesthesia, lethargy, migraine, noncardiac chest pain

Neuromuscular & skeletal: Asthenia, bone fracture, musculoskeletal pain, neck pain, osteoarthritis, tremor

Respiratory: Acute sinusitis, cough, dyspnea, nasal congestion, pneumonia, rhinorrhea

Miscellaneous: Laceration

Implant:

>10%:

Local: Local pain (13%; at implant site), local pruritus (12%; at implant site)

Nervous system: Headache (13%)

1% to 10%:

Cardiovascular: Chest pain (1%)

Dermatologic: Excoriation (1% to 2%; including scratch), localized erythema (10%; at implant site), skin lesion (1%), skin rash (2%)

Gastrointestinal: Constipation (6%), flatulence (1%), nausea (6%), toothache (5%), upper abdominal pain (3%), vomiting (6%)

Hematologic & oncologic: Local hemorrhage (7%; at implant site)

Local: Localized edema (5%; at implant site), local swelling (1%)

Nervous system: Chills (2%), depression (6%), dizziness (4%), drowsiness (3%), fatigue (3%), migraine (2%), pain (4%), paresthesia (1%), sedated state (1%), sensation of cold (1%)

Neuromuscular & skeletal: Asthenia (2%), back pain (6%), limb pain (3%)

Respiratory: Cough (3%), dyspnea (1%), oropharyngeal pain (5%)

Miscellaneous: Fever (3%), laceration (3%)

<1%:

Nervous system: Opioid withdrawal syndrome

Respiratory: Respiratory depression

Injection:

>10%: Nervous system: Sedated state (≤66%)

1% to 10%:

Cardiovascular: Hypotension (1% to 5%)

Dermatologic: Diaphoresis (1% to 5%), injection site pruritus (6% to 10%)

Endocrine & metabolic: Increased gamma-glutamyl transferase (3% to 4%)

Gastrointestinal: Constipation (8% to 9%), nausea (5% to 10%), vomiting (1% to 9%)

Hepatic: Increased serum alanine aminotransferase (1% to 5%), increased serum aspartate aminotransferase (3% to 5%)

Local: Bruising at injection site (1%), erythema at injection site (3% to 4%), induration at injection site (1%), pain at injection site (5% to 6%), swelling at injection site (≤1%)

Nervous system: Dizziness (2% to 10%), drowsiness (2% to 5%), fatigue (4% to 6%), headache (1% to 9%), vertigo (5% to 10%)

Neuromuscular & skeletal: Increased creatine phosphokinase in blood specimen (3% to 5%)

Ophthalmic: Miosis (1% to 5%)

Respiratory: Hypoventilation (1% to 5%)

<1%:

Cardiovascular: Bradycardia, flushing, Mobitz type I second degree atrioventricular block, tachycardia

Dermatologic: Pallor

Gastrointestinal: Diarrhea, xerostomia

Genitourinary: Urinary retention

Local: Cellulitis at injection site, injection site reaction

Nervous system: Abnormal dreams, agitation, confusion, depersonalization, depression, dysphoria, euphoria, local discomfort, localized warm feeling, nervousness, opioid withdrawal syndrome, sensation of cold, slurred speech

Ophthalmic: Amblyopia, blurred vision, conjunctivitis, diplopia, visual disturbance

Otic: Tinnitus

Respiratory: Apnea, cyanosis, dyspnea, respiratory depression

Sublingual tablet:

>10%:

Dermatologic: Diaphoresis (13%)

Gastrointestinal: Abdominal pain (12%), nausea (14%)

Infection: Infection (12%)

Nervous system: Headache (29%), insomnia (21%)

1% to 10%: Gastrointestinal: Constipation (8%), vomiting (8%)

<1%:

Nervous system: Opioid withdrawal syndrome

Respiratory: Respiratory depression

Transdermal patch:

>10%:

Gastrointestinal: Constipation (3% to 13%), nausea (6% to 21%)

Local: Application-site pruritus (5% to 15%)

Nervous system: Dizziness (2% to 15%), drowsiness (2% to 13%), headache (3% to 14%)

1% to 10%:

Cardiovascular: Chest pain (<5%), hypertension (<5%), peripheral edema (1% to <5%)

Dermatologic: Hyperhidrosis (1% to <5%), pruritus (1% to 5%), skin rash (1% to <5%)

Gastrointestinal: Anorexia (1% to <5%), diarrhea (1% to <5%), dyspepsia (1% to <5%), upper abdominal pain (1% to <5%), stomach discomfort (2%), vomiting (≤9%), xerostomia (≥5% to 6%)

Genitourinary: Urinary tract infection (1% to <5%)

Infection: Influenza (1% to <5%)

Local: Application site erythema (5% to 10%), application site irritation (1% to 6%), application site rash (5% to 8%)

Nervous system: Anxiety (1% to <5%), depression (1% to <5%), falling (1% to <5%), fatigue (≤5%), hypoesthesia (1% to <5%), insomnia (<5%), migraine (1% to <5%), pain (1% to <5%), paresthesia (1% to <5%)

Neuromuscular & skeletal: Arthralgia (1% to <5%), asthenia (1% to <5%), back pain (1% to <5%), joint swelling (1% to <5%), limb pain (1% to <5%), muscle spasm (1% to <5%), musculoskeletal pain (1% to <5%), myalgia (1% to <5%), neck pain (1% to <5%), tremor (1% to <5%)

Respiratory: Bronchitis (1% to <5%), cough (1% to <5%), dyspnea (1% to <5%), nasopharyngitis (1% to <5%), pharyngolaryngeal pain (1% to <5%), sinusitis (1% to <5%), upper respiratory tract infection (1% to <5%)

Miscellaneous: Fever (1% to <5%)

<1%:

Cardiovascular: Angina pectoris, facial edema, flushing, hypotension, increased blood pressure, orthostatic hypotension, palpitations, syncope, tachycardia, vasodilation

Dermatologic: Contact dermatitis, xeroderma

Endocrine & metabolic: Decreased libido, dehydration, hot flash, weight loss

Gastrointestinal: Abdominal distention, abdominal pain diverticulitis of the gastrointestinal tract, dysgeusia, dysphagia, flatulence, hiccups, intestinal obstruction

Genitourinary: Sexual disorder, urinary hesitancy, urinary incontinence, urinary retention

Hepatic: Increased serum alanine aminotransferase

Local: Application-site dermatitis

Nervous system: Abnormal gait, agitation, apathy, ataxia, chills, confusion, decreased mental acuity, depressed mood, disorientation, disturbance in attention, dysarthria, emotional lability, euphoria, hallucination, loss of consciousness, malaise, memory impairment, mental status changes, myasthenia, nightmares, opioid withdrawal syndrome, psychosis, restlessness, sedated state, vertigo

Ophthalmic: Miosis, visual disturbance, xerophthalmia

Otic: Tinnitus

Respiratory: Changes in respiration, exacerbation of asthma, hyperventilation, hypoventilation, respiratory depression, respiratory distress, respiratory failure, rhinitis, wheezing

Miscellaneous: Accidental injury

Postmarketing (any route):

Dermatologic: Pruritus, skin necrosis (following inadvertent dermal injection of ER SUBQ injection) (Crouse 2021), skin rash, urticaria

Gastrointestinal: Gallbladder disease (intracholedochal pressure), glossalgia, glossitis, oral hypoesthesia, oral mucosal erythema, stomatitis

Genitourinary: Hypogonadism

Hepatic: Hepatic encephalopathy, hepatic failure, hepatic necrosis, hepatitis (including cytolytic), hepatorenal syndrome, increased serum transaminases, jaundice

Hypersensitivity: Anaphylactic shock, angioedema, hypersensitivity reaction

Local: Application site burning, application site discharge, application site reaction, application site vesicles

Nervous system: Coma, drug dependence (physical dependence), seizure

Respiratory: Bronchospasm

Contraindications

Hypersensitivity (eg, anaphylaxis) to buprenorphine or any component of the formulation.

Buccal film, IR injection, transdermal patch: Additional contraindications: Significant respiratory depression; acute or severe asthma in an unmonitored setting or in the absence of resuscitative equipment; GI obstruction, including paralytic ileus (known or suspected).

Documentation of allergenic cross-reactivity for opioids is limited. However, because of similarities in chemical structure and/or pharmacologic actions, the possibility of cross-sensitivity cannot be ruled out with certainty.

Canadian labeling: Additional contraindications (not in US labeling): Acute respiratory depression; hypercapnia; cor pulmonale; acute alcoholism or current physiological alcohol dependence; delirium tremens; convulsive disorders; severe CNS depression; increased cerebrospinal or intracranial pressure; head injury; severe hepatic insufficiency.

Buccal film, transdermal patch: Additional contraindications: Hypersensitivity to other opioids; suspected surgical abdomen (eg, acute appendicitis or pancreatitis); mild, intermittent or short duration pain that can otherwise be managed; management of acute pain, including use in outpatient or day surgeries; management of perioperative pain relief, or in other situations characterized by rapidly varying analgesic requirements; obstructive airway (other than asthma); status asthmaticus; concurrent use or use within 14 days of monoamine oxidase inhibitors (MAOIs); myasthenia gravis; patients with opioid use disorder and for opioid withdrawal treatment; pregnancy or during labor and delivery; breastfeeding; known or suspected oral mucositis (buccal film only).

ER injection: Additional contraindications: Suspected surgical abdomen (eg, acute appendicitis or pancreatitis); obstructive airway (other than asthma); status asthmaticus; concurrent use with or within 14 days of MAOIs; known or suspected GI obstruction (bowel obstruction or stricture) or any condition affecting bowel transit (ileus of any type); congenital long QT syndrome or QTc prolongation at baseline; uncorrected hypokalemia, hypomagnesemia, hypocalcemia.

Subdermal implant: Additional contraindications: Severe respiratory insufficiency, opioid-naive patients, known or suspected GI obstruction or any condition affecting

bowel transit, congenital long QT prolongation or QTc prolongation at baseline, uncorrected hypokalemia, hypomagnesemia, hypocalcemia.

Warnings/Precautions

Concerns related to adverse effects:

• CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks that require mental alertness (eg, operating machinery, driving).

• Hepatic events: Hepatitis has been reported; hepatic events ranged from transient, asymptomatic transaminase elevations to hepatic failure; in many cases, patients had preexisting hepatic impairment. Monitor LFTs in patients at increased risk for hepatotoxicity (eg, history of alcohol or IV drug abuse, preexisting hepatic dysfunction) prior to and during therapy. Remove buprenorphine subdermal implant if signs and symptoms of buprenorphine toxicity develop concurrent with hepatic impairment. If signs and symptoms of toxicity or overdose occur within 2 weeks of extended-release injection, removal of the depot may be required.

• Hypersensitivity reactions: Hypersensitivity, including bronchospasm, angioneurotic edema, and anaphylactic shock, have been reported. The most common symptoms include rash, hives, and pruritus.

• Hypotension: May cause severe hypotension (including orthostatic hypotension and syncope); use with caution in patients with hypovolemia, cardiovascular disease (including acute myocardial infarction [MI]), or drugs that may exaggerate hypotensive effects (including phenothiazines or general anesthetics). Monitor for symptoms of hypotension following initiation or dose titration. Avoid use in patients with circulatory shock.

• Infection: Subdermal implant: Infection may occur at site of insertion or removal, with excessive palpation shortly after insertion and improper removal increasing the risk. Examine the insertion site 1 week following insertion for signs of infection or problems with wound healing.

• QT prolongation: Buprenorphine has been observed to cause QTc prolongation. Do not exceed a dose of 900 mcg every 12 hours buccal film or one 20 **mcg**/hour transdermal patch. Avoid using in patients with a personal or family history of long QT syndrome or in patients taking concurrent class IA or III antiarrhythmics or other medications that prolong the QT interval. Use with caution in patients with

hypokalemia, hypomagnesemia, or clinically unstable cardiac disease, including unstable heart failure, unstable atrial fibrillation, symptomatic bradycardia, or active MI.

• Respiratory depression: Buccal film, ER and IR injection, transdermal patch: **[US Boxed Warning]: Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely for respiratory depression, especially during initiation or dose escalation. Misuse or abuse by chewing, swallowing, snorting, or injecting buprenorphine extracted from the buccal film or transdermal system will result in the uncontrolled delivery of buprenorphine and pose a significant risk of overdose and death.** Misuse by self-injection of buprenorphine or the concomitant use of buprenorphine and benzodiazepines (or other CNS depressants, including alcohol) may result in coma or death. Carbon dioxide retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids. If the ER injection is discontinued due to respiratory depression, monitor the patient for ongoing respiratory depression for several months due to its ER characteristics. Use with caution in patients with compromised respiratory function (eg, chronic obstructive pulmonary disease, cor pulmonale, decreased respiratory reserve, hypoxia, hypercapnia, or preexisting respiratory depression). Patients and caregivers should be educated on how to recognize respiratory depression and the importance of getting emergency assistance immediately (eg, calling 911) in the event of known or suspected overdose.

Disease-related concerns:

• Abdominal conditions: May obscure diagnosis or clinical course of patients with acute abdominal conditions.

• Adrenocortical insufficiency: Use with caution in patients with adrenal insufficiency, including Addison disease. Long-term opioid use may cause adrenal insufficiency (nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low BP) or secondary hypogonadism, which may lead to mood disorders and osteoporosis (Brennan 2013).

• Biliary tract impairment: Use with caution in patients with biliary tract dysfunction, including acute pancreatitis; opioids may cause constriction of sphincter of Oddi.

• Bowel obstruction: Use with caution in patients with a history of ileus or bowel obstruction; buccal film, IR injection, and transdermal patch are contraindicated in patients with known or suspected GI obstruction, including paralytic ileus.

• CNS depression/coma: Avoid use in patients with impaired consciousness or coma because these patients are susceptible to intracranial effects of CO_2 retention.

• Delirium tremens: Use with caution in patients with delirium tremens.

• Dermatological conditions: Subdermal implant: Use subdermal implants with caution in patients with a history of keloid formation, connective tissue disease (ie, scleroderma), or history of recurrent MRSA infections.

• Head trauma: Use with extreme caution in patients with head injury, intracranial lesions, or elevated intracranial pressure (ICP); exaggerated elevation of ICP may occur. Buprenorphine can produce miosis and changes in the level of consciousness that may interfere with patient evaluation.

• Hepatic impairment: Use buccal film and sublingual tablet with caution in patients with moderate hepatic impairment; dosage adjustment recommended in severe hepatic impairment. Use IR injection with caution in patients with severe impairment. Subdermal implants should not be used in patients with preexisting moderate to severe hepatic impairment. Transdermal patch should not be used in patients with severe hepatic impairment; consider alternative therapy with more flexibility for dosing adjustments. Patients with preexisting moderate or severe hepatic impairment are not candidates for the ER injection. If moderate or severe impairment develops during treatment with the ER injection, continue with caution and monitor for toxicity for several months.

• Obesity: Use with caution in patients who are morbidly obese.

• Oral mucositis: Buccal film: Oral mucositis may lead to more rapid absorption and higher buprenorphine plasma levels; reduce dose in patients with oral mucositis and monitor closely for signs and symptoms of toxicity or overdose.

• Prostatic hyperplasia/urinary stricture: Use with caution in patients with prostatic hyperplasia and/or urinary stricture.

• Psychosis: Use with caution in patients with toxic psychosis.

• Renal impairment: Use with caution in patients with renal impairment.

• Respiratory disease: Use with caution and monitor for respiratory depression in patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or preexisting respiratory depression, particularly when initiating and titrating therapy;

critical respiratory depression may occur, even at therapeutic dosages. Consider the use of alternative nonopioid analgesics in these patients.

• Seizure: Use with caution in patients with a history of seizure disorders; may cause or exacerbate preexisting seizures.

• Sleep-related disorders: Opioid use increases the risk for sleep-related disorders (eg, central sleep apnea [CSA], hypoxemia) in a dose-dependent fashion. Use with caution for chronic pain and titrate dosage cautiously in patients with risk factors for sleep-disordered breathing (eg, heart failure, obesity). Consider dose reduction in patients presenting with CSA. Avoid opioids in patients with moderate to severe sleep-disordered breathing (Dowell [CDC 2016]).

• Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.

Concurrent drug therapy issues:

• Benzodiazepines and other CNS depressants: **[US Boxed Warning]: Buccal film, ER and IR injection, transdermal patch: Concomitant use of benzodiazepines or other CNS depressants, including alcohol and opioids, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing of opioids and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients for signs and symptoms of respiratory depression and sedation.** Prohibiting medication-assisted treatment of opioid use disorder may increase the risk of morbidity and mortality, therefore patients should be educated on the risks of concomitant use with benzodiazepines, sedatives, opioid analgesics, and alcohol. Strategies should be developed to manage use of prescribed or illicit benzodiazepines or other CNS depressants at initiation of or during treatment with buprenorphine; adjustments to induction procedures and additional monitoring may be required. If appropriate, delay or omit buprenorphine dose if a patient is sedated at time of buprenorphine dosing. Discontinuation of benzodiazepines or other CNS depressants is preferred; gradual tapering of benzodiazepine or other CNS depressant, decreasing to lowest effective dose, or monitoring in a higher level of care for taper may be appropriate. Consider prescribing naloxone for emergency treatment of opioid overdose in patients taking benzodiazepines or other CNS depressants concomitantly with opioids. Benzodiazepines are not the treatment of choice for anxiety or insomnia for patients in buprenorphine treatment; make sure patients are

appropriately diagnosed and consider alternative medications for anxiety and insomnia prior to coadministration of benzodiazepines and buprenorphine.

Special populations:

• Cachectic or debilitated patients: Use with caution in cachectic or debilitated patients; there is a greater potential for life-threatening respiratory depression, even at therapeutic dosages. Consider the use of alternative nonopioid analgesics in these patients.

• Elderly: Use with caution in elderly patients; may be more sensitive to adverse effects (eg, life-threatening respiratory depression). In chronic pain, monitor opioid use closely in this age group due to an increased potential for risks, including certain risks such as falls/fracture, cognitive impairment, and constipation (Dowell [CDC 2016]). Consider the use of alternative nonopioid analgesics in these patients.

• Neonates: Neonatal withdrawal syndrome: Buccal film, ER and IR injection, transdermal patch: **[US Boxed Warning]: Prolonged use of opioids during pregnancy can cause neonatal withdrawal syndrome, which may be life-threatening if not recognized and treated according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal withdrawal syndrome and ensure that appropriate treatment will be available.** Signs and symptoms include irritability, hyperactivity and abnormal sleep pattern, high-pitched cry, tremor, vomiting, diarrhea, and failure to gain weight. Onset, duration, and severity depend on the drug used, duration of use, maternal dose, and rate of drug elimination by the newborn.

Dosage form specific issues:

• ER injection: **[US Boxed Warning]: Serious harm or death could result if ER injection is administered IV. The injection forms a solid mass upon contact with body fluids and may cause occlusion, local tissue damage, and thromboembolic events, including life-threatening pulmonary emboli if administered IV. Because of the risk of serious harm or death that could result from IV self-administration, buprenorphine ER injection is only available through a restricted program called the Sublocade REMS Program. Health care settings and pharmacies that order and dispense buprenorphine ER injection must be certified in this program and comply with the REMS requirements.** Injection site reactions (eg, pain, erythema, pruritus), some resulting in abscess, ulceration, or necrosis, have been reported; may require surgical intervention and/or discontinuation of the ER injection. Risk may be

increased with inadvertent IM or intradermal administration. Administer via SUBQ route only; do not administer IM, IV, or intradermally.

• Subdermal implant: **[US Boxed Warning]: Insertion and removal of implant are associated with the risk of implant migration, protrusion, and expulsion. Rare but serious complications including nerve damage and migration resulting in embolism and death may result from improper insertion in the upper arm. Additional complications may include local migration, protrusion, and expulsion. Incomplete insertions or infections may lead to protrusion or expulsion. Because of the risks associated with insertion and removal, buprenorphine implant is available only through a restricted program. All health care providers must successfully complete a live training program on the insertion and removal procedures and become certified, prior to performing insertions or prescribing buprenorphine implants. Patients must be monitored to ensure that the implant is removed by a health care provider certified to perform insertions.**

• Transdermal patch: To properly dispose of transdermal patch, fold it over on itself and flush down the toilet immediately (if a drug take-back option is not readily available); alternatively, seal the used patch in the provided Patch-Disposal Unit and dispose of in the trash. Avoid exposure of application site and surrounding area to direct external heat sources (eg, heating pads, electric blankets, heat or tanning lamps, hot baths/saunas, hot water bottles, direct sunlight). Buprenorphine release from the patch is temperature-dependent and may result in overdose. Patients who experience fever or increase in core temperature should be monitored closely and adjust dose if signs of respiratory depression or CNS depression occur. Application-site reactions, including rare cases of severe reactions (eg, vesicles, discharge, "burns"), have been observed with use; onset varies from days to months after initiation; patients should be instructed to report severe reactions promptly and discontinue therapy.

Special handling:

• Disposal: ER injection and subdermal implant: Handle the removed depots or implants with adequate security, accountability, and proper disposal, per facility procedure for a Schedule III drug product, and per applicable federal, state, and local regulations.

Other warnings/precautions:

• Abrupt discontinuation/withdrawal: Abrupt discontinuation in patients who are physically dependent to opioids has been associated with serious withdrawal

symptoms, uncontrolled pain, attempts to find other opioids (including illicit), and suicide. Use a collaborative, patient-specific taper schedule that minimizes the risk of withdrawal, considering factors such as current opioid dose, duration of use, type of pain, and physical and psychological factors. Monitor pain control, withdrawal symptoms, mood changes, suicidal ideation, and for use of other substances and provide care as needed. Concurrent use of opioid agonist/antagonist analgesics may also precipitate withdrawal symptoms and/or reduced analgesic efficacy in patients following prolonged therapy with mu opioid agonists. Withdrawal signs and symptoms will be delayed in patients who discontinue the ER injection or have it removed; transmucosal buprenorphine may be needed to treat withdrawal in these patients. Tablets, which are used for induction treatment of opioid use disorder, should not be started until objective and clear signs of moderate withdrawal are evident. If subdermal implants are not immediately replaced in contralateral arm after removal, maintain patients on their previous dosage of sublingual buprenorphine.

• Abuse/misuse/diversion: Buccal film, ER and IR injection, transdermal patch: **[US Boxed Warning]: Use exposes patients and other users to the risks of addiction, abuse, and misuse, potentially leading to overdose and death. Assess each patient's risk prior to prescribing; monitor all patients regularly for development of these behaviors or conditions.** Use with caution in patients with a history of substance use disorder; potential for opioid use disorder exists. Other factors associated with an increased risk for misuse include younger age and psychotropic medication use. Consider offering naloxone prescriptions in patients with factors associated with an increased risk for overdose, such as history of overdose or substance use disorder, higher opioid dosages (≥50 morphine milligram equivalents[MME]/day orally), and concomitant benzodiazepine use (Dowell [CDC 2016]). The misuse of buccal film by swallowing or of transdermal patch by placing it in the mouth, chewing it, swallowing it, or using it in ways other than indicated may cause choking, overdose, and death.

• Accidental ingestion: Buccal film, transdermal patch: **[US Boxed Warning]: Accidental ingestion of even one dose, especially in children, can result in a fatal overdose of buprenorphine.**

• Acute pain: When using buprenorphine for treatment of opioid use disorder, treat acute pain with nonopioid analgesics whenever possible. If treatment with a high-affinity full opioid analgesic is required, monitor closely for respiratory depression because high doses may be necessary to achieve pain relief.

• Appropriate use: Buccal film and transdermal patch are indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment; should not be used for as-needed pain relief. Therapy with the buccal film, IR injection, or transdermal patch is not appropriate for use in the management of opioid use disorder. When used for chronic pain (outside of end-of-life or palliative care, active cancer treatment, sickle cell disease, or medication-assisted treatment for opioid use disorder) in outpatient setting in adults, opioids should **not** be used as first-line therapy for chronic pain management (pain >3-month duration or beyond time of normal tissue healing) due to limited short-term benefits, undetermined long-term benefits, and association with serious risks (eg, overdose, MI, auto accidents, risk of developing opioid use disorder). Preferred management includes nonpharmacologic therapy and nonopioid therapy (eg, nonsteroidal anti-inflammatory drugs, acetaminophen, certain anticonvulsants and antidepressants). If opioid therapy is initiated, it should be combined with nonpharmacologic and nonopioid therapy, as appropriate. Prior to initiation, known risks of opioid therapy should be discussed and realistic treatment goals for pain/function should be established, including consideration for discontinuation if benefits do not outweigh risks. Therapy should be continued only if clinically meaningful improvement in pain/function outweighs risks. Therapy should be initiated at the lowest effective dosage using IR opioids (instead of ER/long-acting opioids). Risk associated with use increases with higher opioid dosages. Risks and benefits should be re-evaluated when increasing dosage to ≥50 MME/day orally; dosages ≥90 MME/day orally should be avoided unless carefully justified (Dowell [CDC 2016]).

• Appropriate use: Subdermal implant: Not appropriate for patients who are new to treatment or have not sustained prolonged clinical stability on buprenorphine ≤8 mg/day.

• Discontinuation of therapy: ER injection and sublingual tablet: There is no maximum recommended duration for maintenance treatment of opioid use disorder; patients may require treatment indefinitely. Advise patients of the potential to relapse to illicit drug use following discontinuation of opioid agonist/partial agonist medication-assisted treatment. If the ER injection is discontinued or the depot is removed, monitor the patient for several months for signs and symptoms of withdrawal. After steady-state has been achieved (4 to 6 months), patients discontinuing ER injections may have detectable plasma and urine levels of buprenorphine for 12 months or longer.

• Naloxone access: Discuss the availability of naloxone with all patients who are prescribed opioid analgesics, as well as their caregivers, and consider prescribing it to

patients who are at increased risk of opioid overdose. These include patients who are also taking benzodiazepines or other CNS depressants, have an opioid use disorder (OUD) (current or history of), or have experienced a previous opioid overdose. Additionally, health care providers should consider prescribing naloxone to patients prescribed medications to treat OUD; patients at risk of opioid overdose even if they are not taking an opioid analgesic or medication to treat OUD; and patients taking opioids, including methadone or buprenorphine for OUD, if they have household members, including children, or other close contacts at risk for accidental ingestion or opioid overdose. Inform patients and caregivers on options for obtaining naloxone (eg, by prescription, directly from a pharmacist, a community-based program) as permitted by state dispensing and prescribing guidelines. Educate patients and caregivers on how to recognize respiratory depression, proper administration of naloxone, and getting emergency help.

• Optimal pain regimen: An opioid-containing analgesic regimen should be tailored to each patient's needs and based upon the type of pain being treated (acute versus chronic), the route of administration, degree of tolerance for opioids (naive versus chronic user), age, weight, and medical condition. The optimal analgesic dose varies widely among patients; doses should be titrated to pain relief/prevention.

• Partial opioid agonist and mixed opioid agonist/antagonist overdose: Reversal of partial opioid agonists or mixed opioid agonist/antagonists (eg, buprenorphine, pentazocine) may be incomplete and higher than normal doses and repeated administration of naloxone may be required.

• REMS program: **[US Boxed Warning]: To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, a REMS is required. Drug companies with approved opioid analgesic products must make REMS-compliant education programs available to health care providers. Health care providers are encouraged to complete a REMS-compliant education program; counsel patients and/or their caregivers, with every prescription, on safe use, serious risks, storage, and disposal of these products; emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist; and consider other tools to improve patient, household, and community safety.**

• Surgery: In patients undergoing elective surgery (excluding caesarean section), consider discontinuation of buprenorphine the day before or day of surgery. In patients unable to abruptly discontinue buprenorphine prior to surgery, full opioid

agonists may be added to the buprenorphine to maintain proper analgesia. If opioid therapy is required as part of analgesia, patients should be continuously monitored in an anesthesia care setting by persons not involved in in the conduct of the surgical or diagnostic procedure. The decision whether to discontinue buprenorphine prior to elective surgery should be made in consultation with the surgeon and anesthesiologist. If discontinued, buprenorphine can be resumed postoperatively when there is no longer a need for full opioid agonist therapy; in general, presurgery daily doses may be resumed if held for <2 to 3 days (ASAM 2020).

Metabolism/Transport Effects

Substrate of CYP3A4 (major); **Note:** Assignment of Major/Minor substrate status based on clinically relevant drug interaction potential

Drug Interactions

(For additional information: Launch drug interactions program) Lexicomp®

Abametapir: May increase the serum concentration of CYP3A4 Substrates (High risk with Inhibitors). *Risk X: Avoid combination*

Alcohol (Ethyl): May enhance the CNS depressant effect of Buprenorphine. Management: Advise patients receiving buprenorphine about the increased risk of CNS depression if they consume alcohol. Consider alternatives to buprenorphine for opioid addiction treatment in patients who are dependent on alcohol. *Risk D: Consider therapy modification*

Alizapride: May enhance the CNS depressant effect of CNS Depressants. *Risk C: Monitor therapy*

Alvimopan: Opioid Agonists may enhance the adverse/toxic effect of Alvimopan. This is most notable for patients receiving long-term (i.e., more than 7 days) opiates prior to alvimopan initiation. Management: Alvimopan is contraindicated in patients receiving therapeutic doses of opioids for more than 7 consecutive days immediately prior to alvimopan initiation. *Risk D: Consider therapy modification*

Amphetamines: May enhance the analgesic effect of Opioid Agonists. *Risk C: Monitor therapy*

Anticholinergic Agents: May enhance the adverse/toxic effect of Opioid Agonists. Specifically, the risk for constipation and urinary retention may be increased with this combination. *Risk C: Monitor therapy*

Aprepitant: May increase the serum concentration of CYP3A4 Substrates (High risk with Inhibitors). *Risk C: Monitor therapy*

Atazanavir: Buprenorphine may decrease the serum concentration of Atazanavir. Atazanavir may increase the serum concentration of Buprenorphine. Management: Buprenorphine is not recommended in patients taking atazanavir without ritonavir. In patients taking atazanavir with ritonavir or cobicistat, monitor for opioid excess if coadministered with buprenorphine and consider buprenorphine dose reductions. *Risk X: Avoid combination*

Azelastine (Nasal): May enhance the CNS depressant effect of CNS Depressants. *Risk X: Avoid combination*

Blonanserin: CNS Depressants may enhance the CNS depressant effect of Blonanserin. Management: Use caution if coadministering blonanserin and CNS depressants; dose reduction of the other CNS depressant may be required. Strong CNS depressants should not be coadministered with blonanserin. *Risk D: Consider therapy modification*

Brimonidine (Topical): May enhance the CNS depressant effect of CNS Depressants. *Risk C: Monitor therapy*

Bromopride: May enhance the CNS depressant effect of CNS Depressants. *Risk C: Monitor therapy*

Bromperidol: May enhance the CNS depressant effect of CNS Depressants. *Risk X: Avoid combination*

Cannabinoid-Containing Products: CNS Depressants may enhance the CNS depressant effect of Cannabinoid-Containing Products. *Risk C: Monitor therapy*

Chlormethiazole: May enhance the CNS depressant effect of CNS Depressants. Management: Monitor closely for evidence of excessive CNS depression. The chlormethiazole labeling states that an appropriately reduced dose should be used if such a combination must be used. *Risk D: Consider therapy modification*

Chlorphenesin Carbamate: May enhance the adverse/toxic effect of CNS Depressants. *Risk C: Monitor therapy*

Clofazimine: May increase the serum concentration of CYP3A4 Substrates (High risk with Inhibitors). *Risk C: Monitor therapy*

CNS Depressants: May enhance the CNS depressant effect of Buprenorphine. Management: Consider reduced doses of other CNS depressants, and avoiding such drugs in patients at high risk of buprenorphine overuse/self-injection. Initiate buprenorphine at lower doses in patients already receiving CNS depressants. *Risk D: Consider therapy modification*

CYP3A4 Inducers (Moderate): May decrease the serum concentration of Buprenorphine. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May decrease the serum concentration of Buprenorphine. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May increase the serum concentration of Buprenorphine. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May increase the serum concentration of Buprenorphine. *Risk C: Monitor therapy*

Daclatasvir: May increase the serum concentration of Buprenorphine. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates (High risk with Inducers). *Risk C: Monitor therapy*

Desmopressin: Opioid Agonists may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Dimethindene (Topical): May enhance the CNS depressant effect of CNS Depressants. *Risk C: Monitor therapy*

Diuretics: Opioid Agonists may enhance the adverse/toxic effect of Diuretics. Opioid Agonists may diminish the therapeutic effect of Diuretics. *Risk C: Monitor therapy*

Droperidol: May enhance the CNS depressant effect of CNS Depressants. Management: Consider dose reductions of droperidol or of other CNS agents (eg, opioids, barbiturates) with concomitant use. *Risk D: Consider therapy modification*

Eluxadoline: Opioid Agonists may enhance the constipating effect of Eluxadoline. *Risk X: Avoid combination*

Erdafitinib: May decrease the serum concentration of CYP3A4 Substrates (High risk with Inducers). *Risk C: Monitor therapy*

Erdafitinib: May increase the serum concentration of CYP3A4 Substrates (High risk with Inhibitors). *Risk C: Monitor therapy*

Fexinidazole: May increase the serum concentration of CYP3A4 Substrates (High risk with Inhibitors). *Risk X: Avoid combination*

Flunitrazepam: CNS Depressants may enhance the CNS depressant effect of Flunitrazepam. Management: Reduce the dose of CNS depressants when combined with flunitrazepam and monitor patients for evidence of CNS depression (eg, sedation, respiratory depression). Use non-CNS depressant alternatives when available. *Risk D: Consider therapy modification*

Fosaprepitant: May increase the serum concentration of CYP3A4 Substrates (High risk with Inhibitors). *Risk C: Monitor therapy*

Fusidic Acid (Systemic): May increase the serum concentration of CYP3A4 Substrates (High risk with Inhibitors). *Risk X: Avoid combination*

Gastrointestinal Agents (Prokinetic): Opioid Agonists may diminish the therapeutic effect of Gastrointestinal Agents (Prokinetic). *Risk C: Monitor therapy*

Ivosidenib: May decrease the serum concentration of CYP3A4 Substrates (High risk with Inducers). *Risk C: Monitor therapy*

Kava Kava: May enhance the adverse/toxic effect of CNS Depressants. *Risk C: Monitor therapy*

Lemborexant: May enhance the CNS depressant effect of CNS Depressants. Management: Dosage adjustments of lemborexant and of concomitant CNS depressants may be necessary when administered together because of potentially additive CNS depressant effects. Close monitoring for CNS depressant effects is necessary. *Risk D: Consider therapy modification*

Lisuride: May enhance the CNS depressant effect of CNS Depressants. *Risk C: Monitor therapy*

Lofexidine: May enhance the CNS depressant effect of CNS Depressants. *Risk C: Monitor therapy*

Magnesium Sulfate: May enhance the CNS depressant effect of CNS Depressants. *Risk C: Monitor therapy*

Methotrimeprazine: May enhance the CNS depressant effect of CNS Depressants. CNS Depressants may enhance the CNS depressant effect of Methotrimeprazine. Management:

Reduce the usual dose of CNS depressants by 50% if starting methotrimeprazine until the dose of methotrimeprazine is stable. Monitor patient closely for evidence of CNS depression. *Risk D: Consider therapy modification*

Metoclopramide: May enhance the CNS depressant effect of CNS Depressants. *Risk C: Monitor therapy*

MetyroSINE: CNS Depressants may enhance the sedative effect of MetyroSINE. *Risk C: Monitor therapy*

Minocycline (Systemic): May enhance the CNS depressant effect of CNS Depressants. *Risk C: Monitor therapy*

Monoamine Oxidase Inhibitors: Buprenorphine may enhance the adverse/toxic effect of Monoamine Oxidase Inhibitors. *Risk X: Avoid combination*

Nalmefene: May diminish the therapeutic effect of Opioid Agonists. Management: Avoid the concomitant use of nalmefene and opioid agonists. Discontinue nalmefene 1 week prior to any anticipated use of opioid agonistss. If combined, larger doses of opioid agonists will likely be required. *Risk D: Consider therapy modification*

Naltrexone: May diminish the therapeutic effect of Opioid Agonists. Management: Seek therapeutic alternatives to opioids. See full drug interaction monograph for detailed recommendations. *Risk X: Avoid combination*

Nefazodone: Opioid Agonists (metabolized by CYP3A4) may enhance the serotonergic effect of Nefazodone. This could result in serotonin syndrome. Nefazodone may increase the serum concentration of Opioid Agonists (metabolized by CYP3A4). Management: If concomitant use of opioid agonists that are metabolized by CYP3A4 and nefazodone is necessary, consider dose reduction of the opioid until stable drug effects are achieved. Monitor for increased opioid effects and serotonin syndrome/serotonin toxicity. *Risk D: Consider therapy modification*

Opioid Agonists: Opioids (Mixed Agonist / Antagonist) may diminish the analgesic effect of Opioid Agonists. Management: Seek alternatives to mixed agonist/antagonist opioids in patients receiving pure opioid agonists, and monitor for symptoms of therapeutic failure/high dose requirements (or withdrawal in opioid-dependent patients) if patients receive these combinations. *Risk X: Avoid combination*

Opioids (Mixed Agonist / Antagonist): May diminish the therapeutic effect of Buprenorphine. This combination may also induce opioid withdrawal. *Risk X: Avoid*

combination

Orphenadrine: CNS Depressants may enhance the CNS depressant effect of Orphenadrine. *Risk X: Avoid combination*

Oxomemazine: May enhance the CNS depressant effect of CNS Depressants. *Risk X: Avoid combination*

Paraldehyde: CNS Depressants may enhance the CNS depressant effect of Paraldehyde. *Risk X: Avoid combination*

Pegvisomant: Opioid Agonists may diminish the therapeutic effect of Pegvisomant. *Risk C: Monitor therapy*

PHENobarbital: May enhance the CNS depressant effect of Buprenorphine. PHENobarbital may decrease the serum concentration of Buprenorphine. Management: Avoid use of buprenorphine and phenobarbital when possible. Monitor for respiratory depression/sedation. Because phenobarbital is also a strong CYP3A4 inducer, monitor for decreased buprenorphine efficacy and withdrawal if combined. *Risk D: Consider therapy modification*

Piribedil: CNS Depressants may enhance the CNS depressant effect of Piribedil. *Risk C: Monitor therapy*

Pramipexole: CNS Depressants may enhance the sedative effect of Pramipexole. *Risk C: Monitor therapy*

Primidone: May enhance the CNS depressant effect of Buprenorphine. Primidone may decrease the serum concentration of Buprenorphine. Management: Avoid use of buprenorphine and primidone when possible. Monitor for respiratory depression/sedation. Because primidone is also a strong CYP3A4 inducer, monitor for decreased buprenorphine efficacy and withdrawal if combined. *Risk D: Consider therapy modification*

QT-prolonging Agents (Highest Risk): QT-prolonging Agents (Indeterminate Risk - Avoid) may enhance the QTc-prolonging effect of QT-prolonging Agents (Highest Risk). Management: Monitor for QTc interval prolongation and ventricular arrhythmias when these agents are combined. Patients with additional risk factors for QTc prolongation may be at even higher risk. *Risk C: Monitor therapy*

Ramosetron: Opioid Agonists may enhance the constipating effect of Ramosetron. *Risk C: Monitor therapy*

ROPINIRole: CNS Depressants may enhance the sedative effect of ROPINIRole. *Risk C: Monitor therapy*

Rotigotine: CNS Depressants may enhance the sedative effect of Rotigotine. *Risk C: Monitor therapy*

Rufinamide: May enhance the adverse/toxic effect of CNS Depressants. Specifically, sleepiness and dizziness may be enhanced. *Risk C: Monitor therapy*

Samidorphan: May diminish the therapeutic effect of Opioid Agonists. *Risk X: Avoid combination*

Sarilumab: May decrease the serum concentration of CYP3A4 Substrates (High risk with Inducers). *Risk C: Monitor therapy*

Serotonergic Agents (High Risk): Opioid Agonists (metabolized by CYP3A4) may enhance the serotonergic effect of Serotonergic Agents (High Risk). This could result in serotonin syndrome. Management: Monitor for signs and symptoms of serotonin syndrome/serotonin toxicity (eg, hyperreflexia, clonus, hyperthermia, diaphoresis, tremor, autonomic instability, mental status changes) when these agents are combined. *Risk C: Monitor therapy*

Siltuximab: May decrease the serum concentration of CYP3A4 Substrates (High risk with Inducers). *Risk C: Monitor therapy*

Simeprevir: May increase the serum concentration of CYP3A4 Substrates (High risk with Inhibitors). *Risk C: Monitor therapy*

Sincalide: Drugs that Affect Gallbladder Function may diminish the therapeutic effect of Sincalide. Management: Consider discontinuing drugs that may affect gallbladder motility prior to the use of sincalide to stimulate gallbladder contraction. *Risk D: Consider therapy modification*

Succinylcholine: May enhance the bradycardic effect of Opioid Agonists. *Risk C: Monitor therapy*

Suvorexant: CNS Depressants may enhance the CNS depressant effect of Suvorexant. Management: Dose reduction of suvorexant and/or any other CNS depressant may be necessary. Use of suvorexant with alcohol is not recommended, and the use of suvorexant with any other drug to treat insomnia is not recommended. *Risk D: Consider therapy modification*

Thalidomide: CNS Depressants may enhance the CNS depressant effect of Thalidomide. *Risk X: Avoid combination*

Tocilizumab: May decrease the serum concentration of CYP3A4 Substrates (High risk with Inducers). *Risk C: Monitor therapy*

Zolpidem: CNS Depressants may enhance the CNS depressant effect of Zolpidem. Management: Reduce the Intermezzo brand sublingual zolpidem adult dose to 1.75 mg for men who are also receiving other CNS depressants. No such dose change is recommended for women. Avoid use with other CNS depressants at bedtime; avoid use with alcohol. *Risk D: Consider therapy modification*

Reproductive Considerations

Pregnancy testing is recommended prior to initiating therapy for opioid use disorders. Long-term opioid use and misuse may cause infertility, including erectile dysfunction, decreased sperm motility, menstrual disorders, and amenorrhea in patients of reproductive potential (SAMHSA 2020). Initiation of buprenorphine maintenance treatment may improve fertility resulting in unplanned pregnancy (Dow 2012). Contraception counseling is recommended (Dow 2012; SAMHSA 2020).

Pregnancy Considerations

Buprenorphine crosses the placenta; buprenorphine and norbuprenorphine can be detected in newborn serum, urine, hair, and meconium following in utero exposure (Di Trana 2019).

According to some studies, maternal use of opioids may be associated with birth defects (including neural tube defects, congenital heart defects, and gastroschisis), poor fetal growth, stillbirth, and preterm delivery (CDC [Dowell 2016]). Opioids used as part of obstetric analgesia/anesthesia during labor and delivery may temporarily affect the fetal heart rate (ACOG 209 2019).

[US Boxed Warning]: Prolonged use of opioids during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure appropriate treatment will be available. Symptoms of neonatal abstinence syndrome (NAS) following opioid exposure may be autonomic (eg, fever, temperature instability), gastrointestinal (eg, diarrhea, vomiting, poor feeding/weight gain), or neurologic (eg, high-pitched crying, hyperactivity, increased muscle tone, increased wakefulness/abnormal sleep pattern, irritability, sneezing, seizure, tremor,

yawning) (Dow 2012; Hudak 2012). The risk of neonatal opioid withdrawal is greater following illicit opioid use than when buprenorphine is used as part of a treatment program (ASAM 2020). The onset and duration of neonatal withdrawal symptoms are dependent upon the specific opioid used, maternal dosing, and rate of elimination by the newborn. NAS associated with buprenorphine may correlate to concentrations of norbuprenorphine in the cord blood (Shah 2016). Opioids may cause respiratory depression and psycho-physiologic effects in the neonate; newborns of mothers receiving opioids during pregnancy and/or labor should be monitored.

Opioid agonist pharmacotherapy is recommended for pregnant patients with an opioid use disorder (ACOG 2017; ASAM 2020; SAMHSA 2020). Treatment should begin as early in pregnancy as possible (ASAM 2020). Transmucosal buprenorphine is a recommended treatment option; information related to the use of other dosage forms in pregnancy is limited (ACOG 2017; SAMHSA 2020). Due to pregnancy-induced physiologic changes, some pharmacokinetic properties of sublingual buprenorphine may be altered (Bastian 2017; Caritis 2017; Zhang 2018). Dose adjustments or splitting of a once daily dose may be required in some patients (ASAM 2020). Maintenance doses of buprenorphine will not provide adequate pain relief during labor. Patients receiving buprenorphine for the treatment of opioid use disorder should be maintained on their daily dose of buprenorphine in addition to receiving the same pain management options during labor and delivery as opioid-naive patients; Opioid agonist-antagonists should be avoided for the treatment of labor pain in patients maintained on buprenorphine due to the risk of precipitating acute withdrawal. Use of a multimodal approach to pain relief which can maximize non-opioid interventions is recommended. Monitor for maternal over sedation and somnolence (ACOG 2017; Krans 2019; SAMHSA 2020).

Breast-Feeding Considerations

Buprenorphine is present in breast milk.

Product labeling notes the relative infant dose (RID) of buprenorphine to be <1% when calculated using median breast milk concentrations and compared to weight-adjusted maternal doses following sublingual dosing. In general, breastfeeding is considered acceptable when the RID of a medication is <10% (Anderson 2016; Ito 2000).

The RID of buprenorphine is available from two published studies. One is based on data from six women taking a median sublingual dose of buprenorphine 0.29 mg/kg/day (range: 0.06 to 0.41 mg/kg/day), 5 to 8 days' postpartum. The RID of buprenorphine and the norbuprenorphine metabolite were 0.2% (range: 0.03% to 0.31%) and 0.12% (range: 0.04% to 0.18%) of the weight-adjusted maternal dose, respectively. Breast milk concentrations varied in parallel to the maternal plasma concentrations (Lindemalm 2009). A second study

used data from seven women taking an average sublingual dose of buprenorphine 7 mg/day (range: 2.4 to 24 mg/day), ~1 month postpartum. The mean RID of buprenorphine was calculated to be 0.38% (range: 0.04% to 0.63%) of the weight-adjusted maternal dose, using a mean milk concentration of 3.65 mcg/L (range: 0.83 to 8.27 mcg/L), providing an estimated daily infant dose via breast milk of 0.55 mcg/kg/day (range: 0.12 to 1.24 mcg/kg/day). The mean RID of norbuprenorphine was calculated to be 0.18% (range: 0.03% to 0.31%) of the weight-adjusted maternal dose, using a mean milk concentration of 1.94 mcg/L (range: 0.45 to 4.96 mcg/L), providing an estimated daily infant dose via breast milk of 0.29 mcg/kg/day (range: 0.07 to 0.74 mcg/kg/day) (Ilett 2012). Higher breast milk concentrations of buprenorphine have also been reported following chronic maternal use (Jansson 2016). Buprenorphine and norbuprenorphine were detected in the urine and serum of breasted infants (Jansson 2016; Lindemalm 2009); adverse events were not observed (Ilett 2012; Lindemalm 2009).

Nonopioid analgesics are preferred for breastfeeding patients who require pain control peripartum or for surgery outside of the postpartum period (ABM [Martin 2018]; ABM [Reece-Stremtan 2017]). However, when a narcotic is needed to treat maternal pain following surgery in a breastfeeding patient, use of buprenorphine can be considered. The lowest effective dose for the shortest duration of time should be used to limit adverse events in the mother and breastfeeding infant (ABM [Reece-Stremtan 2017]).

When buprenorphine is used to treat opioid use disorder in breastfeeding patients, most guidelines allow breastfeeding as long as the infant is tolerant to the dose and other contraindications, such as HIV infection or other illicit drug use do not exist (AAP 2012; ABM [Reece-Stremtan 2015]; ACOG 2017; SAMHSA 2020). Breastfeeding can be encouraged for patients on stable maintenance doses, regardless of maternal buprenorphine dose (ABM [Reece-Stremtan 2015]). If additional illicit substances are being abused, patients treated with buprenorphine should express and discard breast milk until sobriety is established (Dow 2012).

The decision to breastfeed during therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and the benefits of treatment to the mother. Breastfeeding patients using opioids for postpartum pain or for the treatment of chronic maternal pain should monitor their infants for drowsiness, sedation, feeding difficulties, or limpness (ACOG 209 2019). Withdrawal symptoms may occur when maternal use is discontinued, or breastfeeding is stopped.

Monitoring Parameters

Pain relief, respiratory and mental status, CNS depression (especially in elderly, debilitated or cachectic patients particularly during treatment initiation or titration, or when using concomitant CNS depressants), blood pressure (monitor for hypotension during initiation and titration); LFTs (prior to initiation and during therapy; monthly for 300 mg maintenance treatment with extended-release injection); pregnancy test (prior to initiation); hepatitis and HIV tests (prior to initiation), particularly for patients with opioid use disorder (SAMHSA 2018); signs of dependence, abuse, or misuse; symptoms of withdrawal; patients with biliary tract disease for worsening symptoms; application site reactions (transdermal patch); signs or symptoms of hypogonadism or hypoadrenalism (Brennan 2013); signs and symptoms of toxicity or overdose (especially in patients with hepatic impairment); signs of infection or problems with wound healing one week after insertion of subdermal implant.

Alternate recommendations: Chronic pain (long-term therapy outside of end-of-life or palliative care, active cancer treatment, sickle cell disease, or medication-assisted treatment for opioid use disorder): Evaluate benefits/risks of opioid therapy within 1 to 4 weeks of treatment initiation and with dose increases. Re-evaluate benefits/risks every 3 months during therapy or more frequently in patients at increased risk of overdose or opioid use disorder. Urine drug testing is recommended prior to initiation and re-checking should be considered at least yearly (includes controlled prescription medications and illicit drugs of abuse). State prescription drug monitoring program data should be reviewed by clinicians prior to initiation and periodically during therapy (frequency ranging from every prescription to every 3 months) (Dowell [CDC 2016]).

Note: Patients undergoing planned surgical procedures, in advance of a procedure, should consult with their buprenorphine prescriber in collaboration with the surgeon, to consider buprenorphine taper and alternative opioid management. Patients undergoing urgent or emergent procedures may require higher than expected opioid doses to achieve adequate analgesia and should be monitored carefully for decreasing opioid requirements as buprenorphine is eliminated. Some patients may achieve adequate analgesia with continued or increased buprenorphine (Alford 2006; Chern 2013; Huang 2014).

Mechanism of Action

Buprenorphine exerts its analgesic effect via high-affinity binding to mu opiate receptors in the CNS; displays partial mu agonist and weak kappa antagonist activity. Due to it being a partial mu agonist, its analgesic effects plateau at higher doses and it then behaves like an antagonist. The extended-release formulation is injected subcutaneously as a liquid; subsequent precipitation following injection results in a solid depot which will gradually release buprenorphine via diffusion and biodegradation of the depot.

Pharmacodynamics and Pharmacokinetics

Onset of action: Analgesic: Immediate-release IM: ≥15 minutes.

Peak effect: Immediate-release IM: ~1 hour.

Duration: Immediate-release IM: ≥6 hours; Extended-release SubQ: 28 days.

Absorption: Immediate-release IM and SubQ: 30% to 40%. Application of a heating pad onto the transdermal system may increase blood concentrations of buprenorphine 26% to 55%. Ingestion of liquids decreases systemic exposure to buprenorphine from buccal film by 23% to 37%.

Distribution: CSF concentrations are ~15% to 25% of plasma concentrations.

V_d:

Premature neonates (GA: 27 to 32 weeks): 6.2 ± 2.1 L/kg (Barrett 1993).

Children 4 to 7 years: 3.2 ± 2 L/kg (Olkkola 1989).

Adults: 97 to 187 L/kg.

Protein binding: High (~96%, primarily to alpha- and beta globulin).

Metabolism: Primarily hepatic via N-dealkylation by CYP3A4 to norbuprenorphine (active metabolite), and to a lesser extent via glucuronidation by UGT1A1 and 2B7 to buprenorphine 3-O-glucuronide; the major metabolite, norbuprenorphine, also undergoes glucuronidation via UGT1A3; extensive first-pass effect.

Bioavailability (relative to IV administration): Buccal film: 46% to 65%; IR IM: 70% (McNicholas 2004); Sublingual tablet: 29% (McNicholas 2004); Transdermal patch: ~15%.

Half-life elimination:

Premature neonates (GA: 27 to 32 weeks): Immediate-release IV: 20 ± 8 hours (Barrett 1993).

Children 4 to 7 years: Immediate-release IV: ~1 hour (Olkkola 1989).

Adults: IV: 2.2 to 3 hours; Buccal film: 27.6 ± 11.2 hours; Apparent terminal half-life: ER injection: 43 to 60 days; Sublingual tablet: ~37 hours; Transdermal patch: ~26 hours. **Note:** Extended elimination half-life for sublingual administration may be due to depot effect (Kuhlman 1996).

Time to peak, plasma: Buccal film: 2.5 to 3 hours; Extended-release SubQ: 24 hours, with steady state achieved after 4 to 6 months; Subdermal implant: 12 hours after insertion, with steady state achieved by week 4; Sublingual: 30 minutes to 1 hour (Kuhlman 1996); Transdermal patch: Steady state achieved by day 3.

Excretion: Feces (~70%; 33% as unchanged drug; 5% as conjugated drug; 21% as norbuprenorphine; and 2% as conjugated norbuprenorphine); urine (27% to 30%; 1% as unchanged drug; 9.4% as conjugated drug; 2.7% as norbuprenorphine; and 11% as conjugated norbuprenorphine).

Clearance: Related to hepatic blood flow.

Premature neonates (GA: 27 to 32 weeks): 0.23 ± 0.07 L/hour/kg (Barrett 1993).

Children 4 to 7 years: 3.6 ± 1.1 L/hour/kg (Olkkola 1989).

Adults: 0.78 to 1.32 L/hour/kg.

Pharmacodynamics and Pharmacokinetics: Additional Considerations

Hepatic function impairment: Because buprenorphine is extensively metabolized, plasma levels and half-life were increased in patients with moderate and severe hepatic impairment.

Geriatric: The pharmacokinetics are similar between younger adults and elderly, although elderly patients showed a trend toward higher plasma concentrations immediately after transdermal system removal.

Pricing: US

Film (Belbuca Buccal)

75 mcg (per each): $7.32

150 mcg (per each): $7.32

300 mcg (per each): $11.51

450 mcg (per each): $15.64

600 mcg (per each): $16.68

750 mcg (per each): $17.54

900 mcg (per each): $18.06

Implant (Probuphine Implant Kit Subcutaneous)

74.2 mg (per each): $1,485.00

Patch weekly (Buprenorphine Transdermal)

5 mcg/hr (per each): $64.43 - $83.24

7.5 mcg/hr (per each): $90.20 - $116.54

10 mcg/hr (per each): $96.64 - $124.87

15 mcg/hr (per each): $139.41 - $180.12

20 mcg/hr (per each): $171.09 - $221.06

Patch weekly (Butrans Transdermal)

5 mcg/hr (per each): $97.23

7.5 mcg/hr (per each): $136.11

10 mcg/hr (per each): $145.84

15 mcg/hr (per each): $210.37

20 mcg/hr (per each): $258.18

Solution (Buprenex Injection)

0.3 mg/mL (per mL): $18.20

Solution (Buprenorphine HCl Injection)

0.3 mg/mL (per mL): $14.34 - $18.20

Solution Prefilled Syringe (Sublocade Subcutaneous)

100 mg/0.5 mL (per 0.5 mL): $2,090.34

300 mg/1.5 mL (per mL): $1,393.56

Sublingual (Buprenorphine HCl Sublingual)

2 mg (per each): $0.37 - $4.53

8 mg (per each): $0.72 - $8.48

Disclaimer: A representative AWP (Average Wholesale Price) price or price range is provided as reference price only. A range is provided when more than one manufacturer's AWP price is available and uses the low and high price reported by the manufacturers to determine the range. The pricing data should be used for benchmarking purposes only, and as such should not be used alone to set or adjudicate any prices for reimbursement or purchasing functions or considered to be an exact price for a single product and/or manufacturer. Medi-Span expressly disclaims all warranties of any kind or nature, whether express or implied, and assumes no liability with respect to accuracy of price or price range data published in its solutions. In no event shall Medi-Span be liable for special, indirect, incidental, or consequential damages arising from use of price or price range data. Pricing data is updated monthly.

Brand Names: International

Acron (BD); Addictex (TR); Addnok (CZ, IN); Bignanto (NO); Brospina (CR, DO, GT, HN, MX, NI, PA, SV); Brospina SL (CR, DO, GT, HN, NI, PA, SV); Bugesic (BD); Bupainx (CZ); Bupensan (EE, LT); Bupine (IN); Buprefarm (NO); Bupren (AR, UA); Buprex (ES); Buprotec (CZ); Butrans (BH, GB, IE, IL, LB); Dorfene (PK); Feliben (ES); Gabup (GB); Hapoctasin (GB); Nalgesic (BD); Nopan (RU); Norphin (IN); Norspan (CN, ES, SK); Norspan Patch (AU, DE, DK, EE, FI, HK, KR, NO, NZ, PH); Norspan Tape (JP); Pentorel (IN); Restiva (AR); Shumeifen (CN); Sovenor (MY, SG); Suboxone (NZ); Subutex (AE, AT, AU, BE, BG, CH, CZ, DE, DK, FR, GR, HR, ID, IE, IL, IS, LU, LV, MT, NO, PT, SE, TW); Temgesic (AE, AT, BE, BF, BJ, BR, CH, CI, CY, DE, DK, EE, EG, ET, FI, FR, GB, GH, GM, GN, GR, HK, IQ, IR, IT, JO, KE, KW, LR, LU, LY, MA, ML, MR, MU, MW, MX, NE, NG, NL, NO, NZ, OM, PK, RU, SA, SC, SD, SE, SG, SK, SL, SN, SY, TN, TR, TW, TZ, UG, YE, ZA, ZM, ZW); Tidigesic (IN); Transtec (BE, CH, CL, CO, DE, DK, EC, ES, GB, HN, HR, HU, IE, IT, MX, NL, NO, PE, PH, PL, PT, SK)

For country abbreviations used in Lexicomp (show table)

REFERENCES

1. *Alford DP, Compton P, Samet JH. Acute pain management for patients receiving maintenance methadone or buprenorphine therapy. Ann Intern Med. 2006;144(2):127-134. [PubMed 16418412]*
2. *Al-Tawil N, Odar-Cederlöf I, Berggren AC, Johnson HE, Persson J. Pharmacokinetics of transdermal buprenorphine patch in the elderly. Eur J Clin Pharmacol. 2013;69(2):143-149. [PubMed 22706617]*
3. *American Academy of Pediatrics (AAP) Section on Breastfeeding. Breastfeeding and the use of human milk. Pediatrics. 2012;129(3):e827-e841. [PubMed 22371471]*
4. *American College of Obstetricians and Gynecologists (ACOG). ACOG practice bulletin no. 209: obstetric analgesia and anesthesia. Obstet Gynecol. 2019;133(3):e208-e225. [PubMed 30801474]*

5. *American College of Obstetricians and Gynecologists (ACOG) Committee on Obstetric Practice. Committee opinion no. 711: opioid use and opioid use disorder in pregnancy. Obstet Gynecol. 2017;130(2):e81-e94. [PubMed 28742676]*
6. *American Society of Addiction Medicine (ASAM). The ASAM national practice guideline for the treatment of opioid use disorder: 2020 focused update. J Addict Med. 2020;14(2S)(suppl 1):1-91. doi:10.1097/ADM.0000000000000633 [PubMed 32511106]*
7. *Anderson PO, Sauberan JB. Modeling drug passage into human milk. Clin Pharmacol Ther. 2016;100(1):42-52. [PubMed 27060684]*
8. *Aurilio C, Ceccarelli I, Pota V, et al. Endocrine and behavioural effects of transdermal buprenorphine in pain-suffering women of different reproductive ages. Endocr J. 2011;58(12):1071-1078. [PubMed 21937837]*
9. *Bailard NS, Ortiz J, Flores RA. Additives to local anesthetics for peripheral nerve blocks: Evidence, limitations, and recommendations. Am J Health Syst Pharm. 2014;71(5):373-385. [PubMed 24534592]*
10. *Barrett DA, Simpson J, Rutter N, Kurihara-Bergstrom T, Shaw PN, Davis SS. The pharmacokinetics and physiological effects of buprenorphine infusion in premature neonates. Br J Clin Pharmacol. 1993;36(3):215-219. [PubMed 9114907]*
11. *Bastian JR, Chen H, Zhang H, et al. Dose-adjusted plasma concentrations of sublingual buprenorphine are lower during than after pregnancy. Am J Obstet Gynecol. 2017;216(1):64.e1-64.e7. [PubMed 27687214]*
12. *Belbuca (buprenorphine) [prescribing information]. Pickering, Ontario, Canada: Purdue Pharma; October 2019.*
13. *Belbuca (buprenorphine) [prescribing information]. Raleigh, NC: BioDelivery Sciences International Inc; March 2021.*
14. *Bliesener N, Albrecht S, Schwager A, Weckbecker K, Lichtermann D, Klingmüller D. Plasma testosterone and sexual function in men receiving buprenorphine maintenance for opioid dependence. J Clin Endocrinol Metab. 2005;90(1):203-206. [PubMed 15483091]*
15. *Brennan MJ. The effect of opioid therapy on endocrine function. Am J Med. 2013;126(3) (Suppl 1):S12-S18. doi: 10.1016/j.amjmed.2012.12.001. [PubMed 23414717]*
16. *Buprenex (buprenorphine) [prescribing information]. North Chesterfield, VA: Indivior Inc; October 2019.*
17. *Buprenorphine sublingual tablets [prescribing information]. Coventry, RI: Rhodes Pharmaceuticals; March 2021.*
18. *Butrans (buprenorphine) [prescribing information]. Stamford, CT: Purdue Pharma; March 2021.*
19. *Butrans (buprenorphine) [product monograph]. Pickering, Ontario, Canada: Purdue Pharma; August 2020.*
20. *Caritis SN, Bastian JR, Zhang H, et al. An evidence-based recommendation to increase the dosing frequency of buprenorphine during pregnancy. Am J Obstet Gynecol. 2017;217(4):459.e1-459.e6. [PubMed 28669739]*
21. *Chern SY, Isserman R, Chen L, Ashburn M, Liu R. Perioperative pain management for patients on chronic buprenorphine: a case report. J Anesth Clin Res. 2013;3(250). [PubMed 24307971]*
22. *Chou R, Fanciullo GJ, Fine PG, et al. Clinical Guidelines For the Use of Chronic Opioid Therapy in Chronic Noncancer Pain. J Pain, 2009, 10(2):113-30. [PubMed 19187889]*

23. *Debono M, Chan S, Rolfe C, Jones TH. Tramadol-induced adrenal insufficiency. Eur J Clin Pharmacol. 2011;67(8):865-867. [PubMed 21243342]*

24. *Di Trana A, La Maida N, Tittarelli R, et al. Monitoring prenatal exposure to buprenorphine and methadone. Ther Drug Monit [published online August 14, 2019]. [PubMed 31425444]*

25. *Dow K, Ordean A, Murphy-Oikonen J, et al. Neonatal Abstinence Syndrome Clinical Practice Guidelines For Ontario. J Popul Ther Clin Pharmacol, 2012, 19(3):e488-506. [PubMed 23241498]*

26. *Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain—United States, 2016. MMWR Recomm Rep. 2016;65(1):1-49. doi: 10.15585/mmwr.rr6501e1. [PubMed 26987082]*

27. *Gowing L, Ali R, White JM, Mbewe D. Buprenorphine for managing opioid withdrawal. Cochrane Database Syst Rev. 2017;2:CD002025. [PubMed 28220474]*

28. *Hall ES, Isemann BT, Wexelblatt SL, et al. A cohort comparison of buprenorphine versus methadone treatment for neonatal abstinence syndrome. J Pediatr. 2016;170:39-44.e1. [PubMed 26703873]*

29. *Hamunen K, Olkkola KT, and Maunuksela EL, "Comparison of the Ventilatory Effects of Morphine and Buprenorphine in Children," Acta Anaesthesiol Scand, 1993, 37(5):449-53. [PubMed 8356856]*

30. *Huang A, Katznelson R, de Perrot M, Clarke H. Perioperative management of a patient undergoing Clagett window closure stabilized on Suboxone® for chronic pain: a case report. Can J Anaesth. 2014;61(9):826-831. [PubMed 24985936]*

31. *Hudak ML, Tan RC. Neonatal drug withdrawal. Pediatrics. 2012;129(2):e540-e560. [PubMed 22291123]*

32. *Ilett KF, Hackett LP, Gower S, Doherty DA, Hamilton D, Bartu AE. Estimated dose exposure of the neonate to buprenorphine and its metabolite norbuprenorphine via breastmilk during maternal buprenorphine substitution treatment. Breastfeed Med. 2012;7:269-274. [PubMed 22011128]*

33. *Ito S. Drug therapy for breast-feeding women. N Engl J Med. 2000;343(2):118-126. [PubMed 10891521]*

34. *Jansson LM, Spencer N, McConnell K, et al. Maternal buprenorphine maintenance and lactation. J Hum Lact. 2016;32(4):675-681. [PubMed 27563013]*

35. *Kampman K, Jarvis M. American Society of Addiction Medicine (ASAM) national practice guideline for the use of medications in the treatment of addiction involving opioid use. J Addict Med. 2015;9(5):358-367. doi:10.1097/ADM.0000000000000166. http://www.asam.org/docs/default-source/practice-support/guidelines-and-consensus-docs/national-practice-guideline.pdf?sfvrsn=18 [PubMed 26406300]*

36. *Kosel J, Bobik P, Siemiątkowski A. Buprenorphine added to bupivacaine prolongs femoral nerve block duration and improves analgesia in patients undergoing primary total knee arthroplasty-a randomised prospective double-blind study. J Arthroplasty. 2015;30(2):320-324. [PubMed 25512031]*

37. *Kraft WK, Adeniyi-Jones SC, Chervoneva I, et al. Buprenorphine for the treatment of the neonatal abstinence syndrome. N Engl J Med. 2017;376(24):2341-2348. [PubMed 28468518]*

38. *Kraft WK, Dysart K, Greenspan JS, et al, "Revised Dose Schema of Sublingual Buprenorphine in the Treatment of the Neonatal Opioid Abstinence Syndrome," Addiction, 2011, 106(3):574-80. [PubMed 20925688]*

39. *Kraft WK, Gibson E, Dysart K, et al, "Sublingual Buprenorphine for Treatment of Neonatal Abstinence Syndrome: A Randomized Trial," Pediatrics, 2008, 122(3):e601-7. [PubMed 18694901]*

40. *Krans EE, Campopiano M, Cleveland LM, et al. National partnership for maternal safety: Consensus bundle on obstetric care for women with opioid use disorder. Obstet Gynecol. 2019;134(2):365-375. [PubMed 31306323]*

41. *Krishnan SH, Gilbert LA, Ghoddoussi F, Applefield DJ, Kassab SS, Ellis TA 2nd. Addition of buprenorphine to local anesthetic in adductor canal blocks after total knee arthroplasty improves postoperative pain relief: a randomized controlled trial. J Clin Anesth. 2016;33:432-437. [PubMed 27555206]*

42. *Kuhlman JJ Jr, Lalani S, Magluilo J Jr, Levine B, Darwin WD. Human pharmacokinetics of intravenous, sublingual, and buccal buprenorphine. J Anal Toxicol. 1996;20(6):369-378. [PubMed 8889672]*

43. *Lindemalm S, Nydert P, Svensson JO, Stahle L, Sarman I. Transfer of buprenorphine into breast milk and calculation of infant drug dose. J Hum Lact. 2009;25(2):199-205. [PubMed 19136395]*

44. *Martin E, Vickers B, Landau R, Reece-Stremtan S. ABM clinical protocol #28, peripartum analgesia and anesthesia for the breastfeeding mother. Breastfeed Med. 2018;13(3):164-171. [PubMed 29595994]*

45. *Maunuksela EL, Korpela R, and Olkkola KT, "Comparison of Buprenorphine With Morphine in the Treatment of Postoperative Pain in Children," Anesth Analg, 1988, 67(3):233-9. [PubMed 3344976]*

46. *Maunuksela EL, Korpela R, and Olkkola KT, "Double-Blind, Multiple-Dose Comparison of Buprenorphine and Morphine in Postoperative Pain of Children," Br J Anaesth, 1988, 60(1):48-55. [PubMed 3337794]*

47. *McNicholas L; US Department of Health and Human Services (HHS). TIP 40: clinical guidelines for the use of buprenorphine in the treatment of opioid addiction: Treatment Improvement Protocol (TIP) series 40. http://lib.adai.washington.edu/clearinghouse/downloads/TIP-40-Clinical-Guidelines-for-the-Use-of-Buprenorphine-in-the-Treatment-of-Opioid-Addiction-54.pdf. Published 2004. Accessed May 11, 2021.*

48. *Ng CM, Dombrowsky E, Lin H, et al. Population pharmacokinetic model of sublingual buprenorphine in neonatal abstinence syndrome. Pharmacotherapy. 2015;35(7):670-680. [PubMed 26172282]*

49. *Olkkola KT, Leijala MA, and Maunuksela EL, "Paediatric Ventilatory Effects of Morphine and Buprenorphine Revisited," Paediatr Anaesth, 1995, 5(5):303-5. [PubMed 7489472]*

50. *Olkkola KT, Maunuksela EL, Korpela R. Pharmacokinetics of intravenous buprenorphine in children. Br J Clin Pharmacol. 1989;28(2):202-204. [PubMed 2775626]*

51. *Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain. 6th ed, Glenview, IL: American Pain Society, 2008.*

52. *Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain. 7th ed. Glenview, IL: American Pain Society; 2016.*

53. *Probuphine (buprenorphine) [prescribing information]. Princeton, NJ: Braeburn Pharmaceuticals Inc; March 2021.*

54. *Probuphine (buprenorphine) [product monograph]. Montreal, Quebec, Canada: Knight Therapeutics Inc; May 2020.*

55. *Reece-Stremtan S, Campos M, Kokajko L; Academy of Breastfeeding Medicine. ABM clinical protocol #15: analgesia and anesthesia for the breastfeeding mother revised 2017. Breastfeed Med. 2017;12(9):500-506. [PubMed 29624435]*

56. *Reece-Stremtan S, Marinelli KA. ABM clinical protocol #21: guidelines for breastfeeding and substance use or substance use disorder, revised 2015. Breastfeed Med. 2015;10(3):135-141. [PubMed 25836677]*

57. *Schnabel A, Reichl SU, Zahn PK, Pogatzki-Zahn EM, Meyer-Friebem CH. Efficacy and safety of buprenorphine in peripheral nerve blocks: A meta-analysis of randomised controlled trials. Eur J Anaesthesiol. 2017. [Epub ahead of print] [PubMed 28368971]*

58. *Shah D, Brown S, Hagemeier N, et al. Predictors of neonatal abstinence syndrome in buprenorphine exposed newborn: can cord blood buprenorphine metabolite levels help? Springerplus. 2016;5(1):854. [PubMed 27386303]*

59. *Soyka M. Buprenorphine Use in Pregnant Opioid Users: A Critical Review. CNS Drugs, 2013, 27(8):653-62. [PubMed 23775478]*

60. *Strain E. Pharmacotherapy for opioid use disorder. Post TW, ed. UpToDate. Waltham, MA: UpToDate Inc. http://www.uptodate.com. Accessed March 3, 2021.*

61. *Sublocade (buprenorphine extended release) [prescribing information]. North Chesterfield, VA: Indivior Inc; June 2021.*

62. *Sublocade (buprenorphine extended release) [product monograph]. Toronto, Ontario, Canada: Pharma Importing Inc; January 2020.*

63. *Substance Abuse and Mental Health Services Administration (SAMHSA). Medications for opioid use disorder: for healthcare and addiction professionals, policymakers, patients, and families. Treatment Improvement Protocol (TIP) Series 63, Full Document. HHS Publication No. (SMA) 19-5063FULLDOC; 2018. Available at https://store.samhsa.gov/sites/default/files/SAMHSA_Digital_Download/PEP20-02-01-006_508.pdf. Accessed February 4, 2021. [PubMed 30566313]*

64. *Substance Abuse and Mental Health Services Administration (SAMHSA). Medications for Opioid Use Disorder. Treatment Improvement Protocol (TIP) Series 63. Publication No. PEP20-02-01-006. Substance Abuse and Mental Health Services Administration; 2020. https://store.samhsa.gov/sites/default/files/SAMHSA_Digital_Download/PEP20-02-01-006_508.pdf. Accessed January 28, 2021.*

65. *Subutex (buprenorphine) [prescribing information]. Richmond, VA: Indivior Inc; March 2021.*

66. *Umbricht A, Hoover DR, Tucker MJ, Leslie JM, Chaisson RE, Preston KL. Opioid detoxification with buprenorphine, clonidine, or methadone in hospitalized heroin-dependent patients with HIV infection. Drug Alcohol Depend. 2003;69(3):263-272. [PubMed 12633912]*

67. *Welsh CJ, Suman M, Cohen A, Broyles L, Bennett M, Weintraub E. The use of intravenous buprenorphine for the treatment of opioid withdrawal in medically ill hospitalized patients. Am J Addict. 2002;11(2):135-140. [PubMed 12028743]*

68. *Zhang H, Kalluri HV, Bastian JR, et al. Gestational changes in buprenorphine exposure: a physiologically-based pharmacokinetic analysis. Br J Clin Pharmacol. 2018;84(9):2075-2087. [PubMed 29873094]*

Topic 9170 Version 429.0

→