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Drugs for Opioid Use Disorder

Note: See addendum

Related article(s) since publication

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Opioid use disorder is a chronic, relapsing disease with physical and psychiatric components. It is associated with economic hardship, social isolation, incarceration, increased rates of blood-borne infections such as HIV and viral hepatitis, adverse pregnancy outcomes, and increased mortality. According to the NIH, there were 80,411 deaths involving an opioid in the US in 2021, more than in any previous year.[1] Several guidelines on the management of opioid use disorder are available; all recommend maintenance pharmacotherapy as the standard of care.[2-5]

METHADONE — A synthetic mu-opioid receptor agonist, methadone suppresses opioid cravings and blocks the euphoric effects of other opioids. It has a slow onset of action and a long, variable elimination half-life. At high doses, it induces cross-tolerance to other opioid agonists. Patients tolerant to other opioid agonists, however, may have incomplete cross-tolerance to methadone.[6]

Availability – Methadone is classified as a schedule II controlled substance (highest potential for abuse; recognized medical use). In the US, methadone maintenance treatment for opioid use disorder is only available through government-licensed opioid treatment programs, which offer supervised administration of the drug. Methadone is available in oral tablets, tablets for oral suspension, an oral solution, and an oral concentrate. To reduce the risk of drug diversion, methadone treatment programs usually do not dispense the tablet formulation.[7]

Key Points: Drugs for Opioid Use Disorder

- Maintenance pharmacotherapy is the standard of care.
- Maintenance treatment with methadone has been shown to reduce mortality, but respiratory depression and drug interactions are a concern.
- Buprenorphine is the maintenance treatment of choice for most patients. It is safer than methadone, can be prescribed in an outpatient setting, and at higher doses appears to be similarly effective.
- Extended-release naltrexone is an alternative for highly motivated patients who do not have access to buprenorphine or methadone or do not want to take an opioid and for those who also have alcohol use disorder. Naltrexone has not been conclusively shown to reduce mortality.
- In pregnant or breastfeeding women, maintenance treatment with methadone or buprenorphine is recommended.
- Naloxone is the drug of choice for emergency treatment of opioid overdose. The FDA has approved over-the-counter sale of naloxone nasal sprays.

Efficacy – Methadone maintenance therapy can improve treatment retention, productivity, and social engagement and decrease crime rates, injection risk behaviors, mortality rates, and the spread of blood-borne infections such as hepatitis C and HIV.[8-12] Use of higher doses of methadone (≥100 mg/day) in patients with opioid use disorder and HIV infection has been associated with increased adherence to antiretroviral therapy, lower viral loads, and higher CD4+ T-cell counts.[13]

Safety – The risk of mortality is highest in the first weeks after starting or stopping methadone treatment.[14] The drug accumulates during induction; it takes 4-7 days to achieve steady state. In overdosage, or if the dose is increased too rapidly, methadone can cause sedation and respiratory depression. The respiratory depressant effect of methadone peaks later and lasts longer than that of buprenorphine and other opioid agonists, and it persists longer than the analgesic effect of the drug. Tolerance can be lost quickly; if a patient misses maintenance doses, the dose should be reduced and

Table 1. Drugs for Maintenance Treatment of Opioid Use Disorder

Drug	Some Available Formulations	Target Maintenance Dosage	Cost[1]
Buprenorphine			
generic	2, 8 mg sublingual tabs	16 mg SL once/day[2]	$132.70
Brixadi (Braeburn)[3]	Weekly: 8 mg/0.16 mL, 16 mg/0.32 mL, 24 mg/0.48 mL, 32 mg/0.64 mL prefilled syringes	24 or 32 mg SC once/week	1660.00
	Monthly: 64 mg/0.18 mL, 96 mg/0.27 mL, 128 mg/0.36 mL prefilled syringes	96 or 128 mg SC q28 days	1595.00
Sublocade (Indivior)[4]	100 mg/0.5 mL, 300 mg/1.5 mL prefilled syringes[5]	100 or 300 mg SC once/month[6]	1920.50
Buprenorphine/Naloxone			
generic	2/0.5, 8/2 mg sublingual tabs, films	16/4 mg SL once/day[2]	184.60[7]
Suboxone (Indivior)	2/0.5, 4/1, 8/2, 12/3 mg sublingual films	16/4 mg SL once/day[2]	538.80
Zubsolv (Orexo)	0.7/0.18, 1.4/0.36, 2.9/0.71, 5.7/1.4, 8.6/2.1, 11.4/2.9 mg sublingual tabs	11.4/2.9 SL mg once/day[2]	588.90
Methadone			
generic	5, 10 mg tabs; 5, 10 mg/5 mL oral solution; 10 mg/mL oral concentrate; 40 mg tabs for oral suspension[8]	80-120 mg PO once/day[9]	99.60[10]
Naltrexone			
generic	50 mg tabs	50 mg PO once/day	53.40
extended-release *Vivitrol* (Alkermes)	380 mg extended-release suspension[5]	380 mg IM once/month	1590.20

1. Approximate WAC for 4 weeks' or 1 month's treatment at the lowest target maintenance dosage. WAC = wholesaler acquisition cost or manufacturer's published price to wholesalers; WAC represents a published catalogue or list price and may not represent an actual transactional price. Source: AnalySource® Monthly. August 5, 2023. Reprinted with permission by First Databank, Inc. All rights reserved. ©2023. www.fdbhealth.com/policies/drug-pricing-policy.
2. Some patients may require maintenance doses of up to 24 mg/day (17.1 mg/day with *Zubsolv*). Data supporting the efficacy of doses >24 mg/day are limited.
3. Approved for treatment of moderate to severe opioid use disorder in patients who have initiated treatment with a single dose of transmucosal buprenorphine product or who are already being treated with buprenorphine.
4. Approved for treatment of moderate to severe opioid use disorder in patients who have received treatment with a transmucosal buprenorphine-containing product for ≥7 days with dose adjustment to 8-24 mg/day of buprenorphine sublingual tablets or equivalent. Not approved for initial treatment.
5. Should be stored in a refrigerator; they should be discarded if left at room temperature for >7 days.
6. 300 mg/month for the first two doses. The 300-mg monthly maintenance dose is recommended if patients do not have a satisfactory clinical response to the 100-mg dose.
7. Cost of sublingual tablets.
8. To reduce the risk of drug diversion, the liquid formulation, diluted in colored water or juice, is generally used in treatment programs.
9. Some rapid metabolizers may require more frequent dosing.
10. Cost of oral concentrate.

retitrated to avoid development of life-threatening respiratory depression.

Methadone can prolong the QT interval and cause arrhythmias such as torsades de pointes, particularly in patients taking high doses (>120 mg/day) or other drugs that prolong the QT interval, and in those with congenital long QT syndrome or a history of QT-interval prolongation.[15] Hypokalemia and cocaine use may also contribute to acquired long QT syndrome.

Drug Interactions – Methadone is a substrate of CYP3A4 and CYP2B6; inhibitors of these isozymes, such as ritonavir, cobicistat, or clarithromycin, can increase serum concentrations of methadone, and inducers, such as rifampin, carbamazepine, or phenytoin, can reduce them.[16] Concurrent use of methadone and other drugs that prolong the QT interval should be avoided if possible.[15] As with any opioid, concomitant use of methadone with selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, or other serotonergic drugs can rarely result in serotonin syndrome. Concurrent use of methadone and benzodiazepines or other sedating drugs can cause additive CNS depression.

Dosage and Administration – In patients with low or no opioid tolerance (e.g., those transitioning from naltrexone), an initial methadone dose of 2.5-10 mg is appropriate. Federal law prohibits administration of an initial methadone dose >30 mg or a total first daily dose >40 mg, unless the physician documents that 40 mg did not suppress opioid abstinence symptoms.[17] Because methadone has a long half-life, the dosage should be titrated cautiously based on the patient's response; a typical timeline might be 10 mg every 5 days. For most patients, a maintenance dose of 60-120 mg/day can suppress cravings and block the euphoric effects of other opioid agonists.[18]

BUPRENORPHINE — A mu-opioid receptor partial agonist and kappa-opioid receptor antagonist, buprenorphine is used alone and in combination with

the opioid antagonist naloxone (*Suboxone*, *Zubsolv*, and generics).[19-21] Taken sublingually, naloxone is poorly absorbed and generally has no clinical effects; combining it with buprenorphine is intended to deter intravenous or intranasal abuse. Two extended-release buprenorphine formulations *(Brixadi, Sublocade)* are FDA-approved for subcutaneous treatment of moderate to severe opioid use disorder.[22,23]

Availability – Buprenorphine is classified as a schedule III controlled substance (less potential for abuse than schedule II; recognized medical use). In the US, federal regulations no longer require prescribers to have a DATA-waiver (X-waiver) to prescribe buprenorphine for opioid use disorder in an outpatient setting.[24] *Brixadi* and *Sublocade* are only available through a Risk Evaluation and Mitigation Strategy (REMS) program.[22,23]

Efficacy – Buprenorphine improves treatment retention and reduces illicit opioid use. It appears to be at least as effective as methadone in reducing mortality.[12,14] Office-based buprenorphine/naloxone maintenance treatment has been shown to improve abstinence rates, occupational stability, and psychosocial outcomes.[25]

Subcutaneous buprenorphine should reduce the risks of treatment nonadherence and drug diversion compared to sublingual formulations, but it is much more expensive.

Safety – Even without naloxone, buprenorphine is safer than methadone because it has a ceiling on its respiratory depressant effect. As a partial agonist, it also has a lower abuse potential than methadone; the presence of naloxone may further reduce the abuse potential of buprenorphine.

Buprenorphine has a greater affinity for opioid receptors than full opioid agonists such as fentanyl and can displace them, causing opioid withdrawal.

Buprenorphine is less likely than methadone to cause cardiac adverse effects. In a retrospective analysis of about 5 million adverse drug events reported to the FDA over 42 years, events mentioning methadone, but not those mentioning buprenorphine, were disproportionately likely to involve QT-interval prolongation, ventricular arrhythmia, or cardiac arrest.[26]

Hepatic impairment reduces naloxone clearance to a greater extent than it does buprenorphine clearance. Use of buprenorphine/naloxone in patients with severe hepatic impairment can lead to withdrawal symptoms when treatment is started and may decrease the efficacy of buprenorphine maintenance.

Injection-site reactions can occur with subcutaneous administration of buprenorphine.

Drug Interactions – Concurrent use of buprenorphine and benzodiazepines or other sedating drugs can result in additive CNS depression. Buprenorphine is metabolized primarily by CYP3A4; use with a 3A4 inducer can decrease buprenorphine serum concentrations and use with a 3A4 inhibitor can increase them. Buprenorphine is also a substrate of P-glycoprotein (P-gp); concomitant use of inhibitors of P-gp could increase buprenorphine serum concentrations.[16] Use of an opioid with serotonergic drugs such as SSRIs may result in serotonin syndrome, though the risk is lower with buprenorphine than it is with directly serotonergic opioids such as methadone.

Buprenorphine can interfere with the analgesic efficacy of full opioid agonists, but current guidelines recommend that patients taking the drug who require surgery continue taking it, with full agonist opioids added as needed.[27]

Dosage and Administration – The risk of serious withdrawal symptoms can be reduced by withholding buprenorphine treatment until the patient is experiencing mild to moderate opioid withdrawal symptoms (Clinical Opiate Withdrawal Scale score ~11-12)[28] and by using a low initial dose (typically 2-4 mg of *Suboxone* or equivalent; some clinicians use as little as 0.5 mg when transitioning from methadone or fentanyl[29]). The daily dose should be uptitrated, usually in increments of 2-8 mg, to 16 mg/day. Some patients may require higher maintenance doses (16-24 mg/day). Data supporting increased efficacy with doses >24 mg/day are limited.[30]

Brixadi can be given once weekly or once monthly; it can be started after a single sublingual dose of buprenorphine and can be stored at room temperature. *Sublocade* is injected once monthly and can be started after 7 days of treatment with sublingual buprenorphine; it should be stored in a refrigerator but can be left at toom temperature up to 7 days before administration.

NALTREXONE — The mu-opioid receptor antagonist naltrexone is available as a once-daily oral tablet and as a once-monthly extended-release microsphere suspension given by intramuscular (IM) injection *(Vivitrol)*. It is not addictive or readily abused,

Table 2. Recommendations for Switching Drugs[1]

Methadone to Buprenorphine
► Tapering to 30-40 mg/day of methadone for about 1 week before transition can reduce patient discomfort
► Wait for mild to moderate withdrawal symptoms to develop before administering the first dose (2-4 mg)
► Observe patient for 1 hour after first dose
► If withdrawal symptoms improve, additional 2- to 8-mg doses can be taken as needed to suppress withdrawal symptoms
Methadone or Buprenorphine to Naltrexone
► Patient must be completely withdrawn from methadone or buprenorphine before starting naltrexone (may take up to 14 days)
► Consider naloxone challenge (0.4-0.8 mg) to confirm absence of physiological dependence, except in pregnant women
Buprenorphine to Methadone
► No special time delay or precautions required
Naltrexone to Buprenorphine or Methadone
► Use of naltrexone can reduce tolerance to opioids
► Administer first dose of methadone or buprenorphine about 1 day after last dose of oral naltrexone or 28 days after last dose of IM naltrexone

1. American Society of Addiction Medicine. The ASAM National Practice Guideline for the Treatment of Opioid Use Disorder: 2020 focused update. J Addict Med 2020; 14(2S Suppl 1):1.

and tolerance to its effects does not develop with long-term use. Both oral and extended-release IM naltrexone are also FDA-approved for treatment of alcohol use disorder.[31]

Availability – Naltrexone is not a controlled substance, and there are no special restrictions on its prescription.

Efficacy – Adherence and outcomes are better with once-monthly **IM naltrexone** than with the oral formulation. IM naltrexone has been shown to improve abstinence rates and retention in treatment programs and to reduce cravings and relapse to physiological dependence.[32,33] In a 24-week, open-label study in 570 patients, treatment failure during induction occurred significantly more often with once-monthly IM naltrexone than with sublingual buprenorphine/naloxone, but among those who were successfully inducted, the two treatments were similar in efficacy and safety.[34] In a 12-week, open-label study in 159 patients in Norway, abstinence and treatment retention rates with IM naltrexone were noninferior to those with sublingual buprenorphine/naloxone.[35] Whether use of IM naltrexone can reduce the risk of death remains to be determined; in one meta-analysis of 30 cohort studies, patients treated with the drug had lower rates of death from overdose and from all causes.[36]

In a meta-analysis of 13 studies, **oral naltrexone** was not more effective than placebo, nonpharmacologic treatment, benzodiazepines, or buprenorphine in reducing opioid use, and treatment retention was poor.[37] Oral naltrexone was more effective than placebo in sustaining abstinence in studies where patients were legally mandated to take the drug.[32,37,38]

Safety – Naltrexone is generally well tolerated. Adverse effects of IM naltrexone have included injection-site reactions, hepatic enzyme elevations, nasopharyngitis, insomnia, headache, nausea, and toothache. Depressed mood and suicidality have occurred rarely; a causal relationship has not been established. Hepatotoxicity has been reported with use of naltrexone, but it is also associated with opioid and alcohol use disorders themselves. Naltrexone can reduce tolerance to opioids; patients who relapse after receiving naltrexone may be at greater risk of a serious, potentially fatal opioid overdose.

Drug Interactions – Naltrexone blocks the effects of opioids, including opioid-derivative antidiarrheals and antitussives.[39] It should not be used in patients taking an opioid for treatment of pain. Oral naltrexone should be stopped 72 hours before and IM naltrexone 30 days before elective surgery.

Dosage and Administration – Administration of naltrexone to a patient with physiological opioid dependence can precipitate a severe opioid withdrawal syndrome; patients should be free of dependence for at least 7 days before naltrexone is started. A naloxone challenge can be used to confirm the absence of physiological opioid dependence. Patients starting treatment with oral naltrexone should receive an initial dose of 25 mg. If withdrawal symptoms do not occur, a maintenance dosage of 50 mg once daily can be given.

Vivitrol should be given as a deep intragluteal injection in alternating buttocks every 4 weeks or once monthly. The drug should be stored in a refrigerator, but it can be left unrefrigerated for up to 7 days as long as it is not exposed to temperatures >77°F (25°C).

ALTERNATIVES — Limited data suggest that **24-hour extended-release oral morphine** (off-label) may be effective for maintenance treatment of opioid use disorder. Morphine may be better tolerated and more effective than methadone in some patients but it may increase the risk of opioid-related adverse effects.[40]

In a meta-analysis of 4 randomized trials, rates of heroin use and treatment retention with extended-release oral morphine were similar to those with methadone, but the trials were judged to be low to moderate in quality.[41]

Addition of supervised **heroin** injections to flexible-dose methadone therapy has been shown to improve treatment retention and may reduce criminal activity, incarceration rates, and social functioning, but it also increases the risk of adverse events.[42]

In a 12-week, randomized, double-blind trial in 196 patients with opioid use disorder, addition of the antitussive **dextromethorphan** 60 mg/day to methadone maintenance treatment significantly improved treatment retention and decreased plasma morphine levels compared to placebo, but addition of dextromethorphan 120 mg/day did not.[43]

In a 24-week randomized trial in 141 patients with opioid use disorder, addition of **cognitive behavioral therapy** to primary care-based maintenance treatment with buprenorphine did not improve rates of self-reported opioid use or opioid abstinence.[44]

PREGNANCY — Opioid use during pregnancy is associated with an increased risk of complications including preeclampsia, miscarriage, reduced fetal growth, fetal death, and premature delivery. Pregnant women with opioid use disorder should receive maintenance treatment with methadone or buprenorphine.[45]

Methadone has a long history of use in pregnancy and is generally considered the standard of care for maintenance treatment of pregnant women with opioid use disorder. More recently, **buprenorphine** has been used as an effective and safe alternative. In a randomized, double-blind, double-dummy trial in 175 pregnant women with opioid use disorder, neonates whose mothers were treated with buprenorphine during pregnancy required less morphine and had shorter durations of treatment for neonatal abstinence syndrome and shorter hospital stays than those whose mothers received methadone, but treatment retention was significantly greater among women taking methadone.[46]

Combination **buprenorphine/naloxone** products are considered safe for use during pregnancy, but data on their efficacy in pregnant women are limited.[47]

Data on the safety and efficacy of **naltrexone** use in pregnancy are also limited. In general, women taking naltrexone who become pregnant and are at high risk for relapse can continue treatment. Use of challenge doses of naltrexone to test for physiological opioid dependence is contraindicated because it can induce preterm labor and fetal distress.

LACTATION — Use of **methadone** or **buprenorphine** monotherapy by breastfeeding women is generally considered safe.[2] Transfer of **naltrexone** through breast milk appears to be minimal, but clinical data are sparse.[48]

TREATMENT OF OPIOID OVERDOSE

Two opioid antagonists, naloxone and nalmefene, are available for reversal of opioid overdose. The goal of treatment is adequate ventilation. If not already present, emergency medical services should be called immediately after administration of naloxone or nalmefene.

NALOXONE — Naloxone is the drug of choice for emergency treatment of opioid overdose. It is available in various dosage forms for intravenous, intramuscular, subcutaneous, or intranasal administration (see Table 3).[49-51]

Availability – Every state in the US now has a naloxone access law; in most states, these laws grant both civil and criminal immunity to laypersons who administer naloxone.[52] The US Department of Health and Human Services has recommended that certain individuals who are prescribed opioids or are at high risk for an opioid overdose, their caregivers, and persons who are likely to respond to an overdose event carry naloxone nasal spray (see Table 4).[53]

The FDA has approved the over-the-counter (OTC) sale of three naloxone nasal sprays (*Narcan*, one of its generics, and *RiVive*), but none of these products are currently available OTC. Announcements about their availability and cost are expected in the coming months.[54,55]

Pharmacology – Naloxone is a competitive mu-opioid receptor antagonist. In opioid overdose, it begins to reverse sedation, respiratory depression, and hypotension within 1-2 minutes after IV administration, 2-5 minutes after IM or SC administration, and 8-13 minutes after intranasal administration.

The half-life of naloxone (1 to 2 hours) is much shorter than that of most opioids; repeated administration may be necessary, especially for treatment of overdose with a long-acting opioid or an extended-release opioid formulation.[56]

Table 3. Drugs for Reversal of Opioid Overdose[1]

Drug	Formulations	Usual Dosage	Cost[2]
Nalmefene HCl			
generic (Purdue)	2 mg/2 mL vials	0.5 mg/70 kg IV[3]	$30.00[4]
Opvee (Opiant)	2.7 mg/0.1 mL nasal spray	2.7 mg intranasally[5]	N.A.
Naloxone			
generic	0.4 mg/mL vials, syringes	0.4-2 mg IV, IM, or SC[6]	10.70[7]
LifEMS Naloxone (Lifsa)	2 mg/2 mL syringes	2 mg IV, IM, or SC[6]	1678.00
Zimhi (Adamis)	5 mg/0.5 mL syringes	5 mg IM or SC[5]	62.50
RiVive (Harm Reduction)[8]	3 mg/0.1 mL nasal spray	3 mg intranasally[5]	N.A.
generic[8] *Narcan* (Emergent)[8]	4 mg/0.1 mL nasal spray	4 mg intranasally[5]	54.80 62.50
Kloxxado (Hikma)	8 mg/0.1 mL nasal spray	8 mg intranasally[5]	62.50

N.A.= cost not yet available

1. The goal of treatment is adequate ventilation.
2. Approximate WAC for one dose at the lowest recommended dosage. WAC = wholesaler acquisition cost or manufacturer's published price to wholesalers; WAC represents a published catalogue or list price and may not represent an actual transactional price. Source: AnalySource® Monthly. August 5, 2023. Reprinted with permission by First Databank, Inc. All rights reserved. ©2023. www.fdbhealth.com/drug-pricing-policy.
3. If a clinical response is not observed after the initial dose, a second dose of 1 mg/70 kg can be given 2-5 minutes later. Total doses >1.5 mg/70 kg are unlikely to improve clinical response. When IV access is not possible, a single IM or SC dose of 1 mg is an alternative. According to the label, if opioid dependency is suspected, a challenge dose of 0.1 mg/70 kg should be administered initially; if there is no evidence of withdrawal in 2 minutes, the recommended dosing should be followed.
4. Cost of a 2-mL vial.
5. Dose can be repeated every 2-5 minutes (nalmefene) or every 2-3 minutes (naloxone) until the patient responds or emergency medical personnel arrive.
6. IV administration is preferred. Dose can be repeated every 2-3 minutes up to a total of 10 mg. Depending on the clinical presentation, lower doses titrated to effect (adequate ventilation without precipitation of withdrawal) are often used in an acute-care setting.
7. Cost of a 1-mL vial.
8. *Narcan*, one of its generics, and *RiVive* have been approved for sale over the counter. Announcements about their OTC availability and cost are expected in the coming months.

Adverse Effects – Whether naloxone itself has any toxicity is unclear, but it can precipitate acute withdrawal symptoms in opioid-dependent patients. Acute opioid withdrawal is associated with anxiety, piloerection, yawning, sneezing, rhinorrhea, nausea, vomiting, diarrhea, and abdominal or muscle cramps, which are uncomfortable but generally not life-threatening, except in neonates. In a pharmacokinetic study, the most common adverse effects of intranasal naloxone were increased blood pressure, constipation, toothache, muscle spasms, musculoskeletal pain, headache, xeroderma, rhinalgia, and other intranasal effects including dryness, edema, congestion, and inflammation. Reversal of opioid overdose could unmask the sympathomimetic effects of stimulant drugs in cases of mixed overdose.

Table 4. Persons Who Should Carry Naloxone[1,2]

Patients prescribed opioids who:

- Are taking ≥50 morphine milligram equivalents (MME) per day
- Have respiratory conditions such as chronic obstructive pulmonary disease (COPD) or obstructive sleep apnea (regardless of opioid dose)
- Have been prescribed benzodiazepines (regardless of opioid dose)
- Have a non-opioid substance use disorder, report excessive alcohol use, or have a mental health disorder (regardless of opioid dose)

Other persons in high-risk situations, including those:

- Using heroin or illicit synthetic opioids or misusing prescription opioids
- Using other illicit drugs such as methamphetamine or cocaine that could potentially be contaminated with illicit synthetic opioids such as fentanyl
- Receiving treatment for opioid use disorder
- With a history of opioid misuse who were recently released from incarceration or other controlled settings and are no longer tolerant to opioids
- Living or spending time with people who use drugs
- With children in the same house as prescription opioids

1. HHS. Naloxone: the opioid reversal drug that saves lives. Available at: https://bit.ly/3k68NiV. Accessed August 17, 2023.
2. Includes at-risk individuals, their caregivers, and those likely to respond to an overdose event.

Pregnancy – No embryotoxic or teratogenic effects were observed with use of large doses of naloxone in pregnant mice and rats. Naloxone does cross the placenta, however, and may cause fetal opioid withdrawal or induce preterm labor.

NALMEFENE – The opioid antagonist nalmefene is FDA-approved as a nasal spray *(Opvee)* and an injectable solution for treatment of known or suspected opioid overdose.[57,58] It has a longer duration of action than many opioid analgesics (half-life ~11 hours), and it could precipitate a period of withdrawal in patients dependent on opioids. Clinical data are lacking on use of nalmefene for reversal of overdose due to fentanyl or its analogs.

Availability – Nalmefene is only available by prescription. In most, but not all states, access laws that grant civil or criminal immunity to laypersons who administer naloxone appear to also apply to other opioid antagonists such as nalmefene.[52]

Adverse Effects – Adverse effects of nalmefene include nausea, vomiting, tachycardia, hypertension, fever, and dizziness. The nasal spray can also cause nasal discomfort and headache. Reversal of opioid overdose could unmask the sympathomimetic effects of stimulant drugs in cases of mixed overdose.

Pregnancy – No human data are available on use of nalmefene during pregnancy. Use of high doses of the drug in pregnant rats and rabbits did not result in embryotoxic effects. ■

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ADDENDUM

Over-the-Counter *Narcan* Nasal Spray

Since the publication of our articles entitled Drugs for Opioid Use Disorder and In Brief: Over-the-Counter Narcan Nasal Spray earlier this year, *Narcan* (Emergent), a nasal spray that delivers 4 mg of the opioid antagonist naloxone, has become available for sale over the counter (OTC). According to the manufacturer, the retail price for a box containing 2 doses is $44.99. Some insurance companies have announced plans to cover OTC purchase of the drug for their members.

RiVive (Harm Reduction Therapeutics), a 3-mg naloxone nasal spray recently FDA-approved for OTC sale, is expected to be marketed early next year. ■

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The expected outcome of the CME program is to increase the participant's knowledge about, or apply knowledge into practice after assimilating, information presented in materials contained in The Medical Letter.

The Medical Letter will strive to continually improve the CME program through periodic assessment of the program and activities. The Medical Letter aims to be a leader in supporting the professional development of healthcare providers by providing continuing medical education that is unbiased and free of pharmaceutical industry influence. The Medical Letter does not sell advertising or receive any commercial support.

GOAL:

Through this program, The Medical Letter expects to provide the healthcare community with unbiased, reliable, and timely educational content that they will use to make independent and informed therapeutic choices in their practice.

DISCLOSURE:

Principal Faculty for this Activity:

Mark Abramowicz, M.D., President has disclosed no relevant financial relationships
Jean-Marie Pflomm, Pharm.D., Editor in Chief has disclosed no relevant financial relationships
Brinda M. Shah, Pharm.D., Consulting Editor has disclosed no relevant financial relationships.

In addition to the Principal Faculty above, the following have also contributed to this activity:
Michael Viscusi, Pharm.D., Associate Editor has disclosed no relevant financial relationships.

LEARNING OBJECTIVES FOR THIS ACTIVITY:

Activity participants will read and assimilate unbiased reviews of FDA-approved and off-label uses of drugs and other treatment modalities. Activity participants will be able to select and prescribe, or confirm the appropriateness of the prescribed usage of, the drugs and other therapeutic modalities discussed in *The Medical Letter* with specific attention to clinical trials, pathophysiology, dosage and administration, drug metabolism and interactions, and patient management. Activity participants will make independent and informed therapeutic choices in their practice.

Upon completion of this activity, the participant will be able to:

1. Explain the current approach to treatment of opioid use disorder.
2. Discuss the pharmacological options available for treatment of opioid use disorder and compare them based on their efficacy, safety, potential drug interactions, and availability.
3. Determine the best course of treatment for an individual patient with opioid use disorder.

CREDIT:

Participants who complete this activity and achieve a score of 70% or higher on the post-activity exam will be awarded 2 credits.

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Note: The participant should read the post-activity questions prior to beginning the activity. After careful review of the text, tables, and cited references, the participant should take time to reflect on how the newly acquired knowledge will be applied to clinical practice, affect patient care, and improve outcomes.

Issue 1684 Post-Activity Questions

(Correspond to questions #41-50 in Comprehensive Activity #89, available January 2024)

Drugs for Opioid Use Disorder

1. The standard of care for treatment of opioid use disorder is:
   a. group psychosocial therapy
   b. managed withdrawal followed by psychosocial therapy
   c. maintenance pharmacotherapy
   d. as-needed use of a benzodiazepine

2. Methadone maintenance treatment can:
   a. suppress cravings
   b. block the euphoric effects of other opioid agonists
   c. decrease mortality rates
   d. all of the above

3. Methadone:
   a. is a schedule II controlled substance
   b. can prolong the QT interval
   c. interacts with drugs that induce or inhibit CYP3A4
   d. all of the above

4. Buprenorphine is available in sublingual formulations alone and in combination with:
   a. methadone
   b. naloxone
   c. naltrexone
   d. nalmefene

5. Buprenorphine can improve:
   a. abstinence rates
   b. occupational stability
   c. mortality rates
   d. all of the above

6. Buprenorphine can cause:
   a. QT-interval prolongation
   b. nephrotoxicity
   c. opioid withdrawal
   d. all of the above

7. Oral naltrexone:
   a. can precipitate withdrawal in patients with physiological opioid dependence
   b. is more effective than the intramuscular formulation for treatment of opioid use disorder
   c. is a controlled substance
   d. all of the above

8. The goal of treatment of opioid overdose with naloxone is:
   a. full alertness
   b. systolic blood pressure >100 mm Hg
   c. adequate ventilation
   d. all of the above

9. The FDA has approved over-the-counter sale of naloxone:
   a. tablets
   b. nasal spray
   c. intramuscular injection
   d. subcutaneous injection

10. Naloxone:
    a. is a competitive mu-opioid receptor antagonist
    b. can precipitate acute withdrawal symptoms in opioid-dependent patients
    c. has a much shorter half-life than most opioids
    d. all of the above

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Successful completion of the post-test is required to earn AAPA Category 1 CME credit. Successful completion is defined as a cumulative score of at least 70 percent correct.