Therapeutic Class Overview
Opioid Use Disorder Agents

INTRODUCTION

Products for Treatment of Opioid Dependence

- The American Psychiatric Association (APA) defines opioid use disorder as a syndrome characterized by a problematic pattern of opioid use, leading to clinically significant impairment or distress (*APA 2013*).
  - In 2015, approximately 2 million Americans had a substance use disorder involving prescription pain relievers and 591,000 had a substance use disorder involving heroin (*American Society of Addiction Medicine [ASAM] 2016*).
- Methadone, buprenorphine (with or without naloxone), and naltrexone are Food and Drug Administration (FDA)-approved for the detoxification and maintenance treatment of opioid dependence (*Micromedex 2021*).
  - Methadone products, when used for the treatment of opioid addiction in detoxification or maintenance programs, may be dispensed only by opioid treatment programs (and agencies, practitioners, or institutions by formal agreement with the program sponsor) certified by the Substance Abuse and Mental Health Services Administration (SAMHSA) and approved by the designated state authority. Certified treatment programs may dispense and use methadone in oral form only and according to the treatment requirements stipulated in the Federal Opioid Treatment Standards (Code of Federal Regulations, Title 42, Sec 8).
  - The Drug Addiction Treatment Act (DATA) of 2000 expanded the clinical context of medication-assisted opioid addiction treatment by allowing qualified physicians to dispense or prescribe specifically approved medications, like buprenorphine, for the treatment of opioid addiction in treatment settings other than the traditional Opioid Treatment Program. In addition, DATA reduced the regulatory burden on physicians who choose to practice opioid addiction therapy by permitting qualified physicians to apply for and receive waivers of the special registration requirements defined in the Controlled Substances Act (*SAMHSA statutes, regulations, and guidelines 2021*).
  - Naltrexone, an opioid antagonist, is only indicated for the prevention of relapse after opioid detoxification; patients must be opioid-free for at least 7 to 10 days prior to initiation of naltrexone therapy in order to avoid precipitation of withdrawal.
- All buprenorphine products are Schedule III controlled substances (*Drugs@FDA 2021*).
- In 2012, Reckitt Benckiser Pharmaceuticals notified the FDA that they were voluntarily discontinuing production of Suboxone (buprenorphine/naloxone) sublingual tablets as a result of increasing concerns over accidental pediatric exposure with the tablets; the unique child-resistant, unit-dose packaging of the film formulation is believed to be a contributing factor to reduce exposure rates in children. Generic formulations of the sublingual tablets remain available.
- In November 2017, the FDA approved Sublocade (buprenorphine ER) SC injection for the treatment of moderate to severe opioid use disorder in patients who have initiated treatment with a transmucosal buprenorphine-containing product, followed by dose adjustment for a minimum of 7 days.
  - Sublocade is injected as a liquid and the subsequent precipitation of the polymer creates a solid depot, which contains buprenorphine. Buprenorphine is released via diffusion from, and the biodegradation of, the depot.
- On September 7, 2018, a new dosage strength of buprenorphine/naloxone sublingual films was approved by the FDA under the brand name Cassipa. However, the launch of this product has been delayed due to patent infringement claims made by the manufacturer of Suboxone. The current estimated launch date of Cassipa is unknown, and the FDA shows that the product has been discontinued (*Drugs@FDA 2021*).
- Lofexidine, an oral central alpha-2 agonist, was approved in May 2018 for the mitigation of opioid withdrawal symptoms to facilitate abrupt opioid discontinuation in adults. This product is indicated for short-term use, up to 14 days, during the period of peak opioid withdrawal symptoms.
- Included in this review are the products that are FDA-approved to be used in the treatment of opioid dependence; however, methadone products are not included since they must be dispensed in an opioid treatment program when used for the treatment of opioid addiction in detoxification.
- Medispan Class: Opioid Use Disorder Agents; Agents for Chemical Dependency

Table 1. Medications for Treatment of Opioid Dependence Included Within Class Review

Drug	Generic Availability
Single-Entity Agents	
buprenorphine* sublingual tablet	✔
Lucemyra (lofexidine) tablet	-
naltrexone hydrochloride (HCl)* tablet	✔
Sublocade (buprenorphine) subcutaneous (SC) injection	-
Vivitrol (naltrexone) intramuscular (IM) injection	-
Combination Products	
Bunavail (buprenorphine/naloxone) buccal film‡	-
buprenorphine/naloxone* sublingual tablets	✔
Suboxone (buprenorphine/naloxone) sublingual film	✔
Zubsolv (buprenorphine/naloxone) sublingual tablets	-

* Brand name product was discontinued; however, generic formulations are available.
‡ Product was discontinued; the expiration dates of the last manufactured batches range from February to October 2021.

(*Drugs@FDA 2021, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2021*)

Products for Emergency Treatment of Opioid Overdose

- Opiate overdose continues to be a major public health problem in the United States (U.S.). It has contributed significantly to accidental deaths among those who use or abuse illicit and prescription opioids. Overdose deaths involving opioids accounted for more than 70% of the nearly 71,000 drug overdose deaths in 2019, exceeding the number of deaths caused by motor vehicle crashes (*Centers for Disease Control and Prevention 2021*).
- Death following opioid overdose can be averted by emergency basic life support and/or the timely administration of an opioid antagonist such as naloxone. Naloxone is a narcotic antagonist that displaces opiates from receptor sites in the brain and reverses respiratory depression, which is usually the cause of overdose deaths (*SAMHSA 2018, World Health Organization [WHO] 2014*).
- Naloxone is provided to patients through the regular course of medical care, by pharmacist-initiated collaborative practice agreements, or through community-based opioid overdose prevention programs (*Doe-Simkins 2014*).
- Recognizing the potential value of providing naloxone to laypersons, most states have passed laws and changed regulations authorizing prescribers to provide naloxone through standing orders and/or to potential overdose witnesses as well as protecting those who administer naloxone from penalties for practicing medicine without a license (*Morbidity and Mortality Weekly Report [MMWR] 2012, Coffin 2021*).
- In December 2018, the U.S. Department of Health & Human Services (HHS) recommended prescribing or co-prescribing naloxone to all patients who are at risk for opioid overdose, including: patients receiving opioids at a dosage of 50 milligram morphine equivalents (MME) per day or greater; patients with respiratory conditions who are prescribed opioids; patients who have been prescribed benzodiazepines along with opioids; and patients prescribed opioids who have a non-opioid substance use disorder, report excessive alcohol use, or have a mental health disorder (*HHS 2018*).
- In patients with opioid overdose, naloxone begins to reverse sedation, respiratory depression, and hypotension within 1 to 2 minutes after intravenous (IV) administration, 2 to 5 minutes after IM or SC administration, and 8 to 13 minutes after intranasal (IN) administration. Since the half-life of naloxone is much shorter than that of most opioids, repeated administration may be necessary (*Lexicomp 2021)*.
- Naloxone was first approved by the FDA in 1971. In November 2015, the FDA approved the first IN formulation of naloxone (Narcan nasal spray). Prior to the approval of these products, naloxone was only available in glass vials and ampules, which were distributed with syringes and needles for manual injection or with syringes and atomizers for off-label IN administration.
- Included in this review are the naloxone products that are FDA-approved for opioid overdose.
- Medispan Class: Opioid Antagonists

Table 2. Medications for Emergency Treatment of Opioid Overdose Included Within Class Review

Drug	Generic Availability
naloxone HCl* injection	✔
Narcan (naloxone HCl) nasal spray	-†
Kloxxado, (naloxone HCl) nasal spray	-

* Brand name product was discontinued; however, generic formulations are available.
† Generic product for Narcan approved by the FDA, but not yet launched due to patent litigation.

(*Drugs@FDA 2021, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2021*)

INDICATIONS

Table 3. FDA-Approved Indications for Buprenorphine and Buprenorphine/Naloxone Products

Indication	Single-Entity Agents		Combination Products			
	Sublocade (buprenorphine) SC injection	buprenorphine sublingual tablets	Bunavail (buprenorphine/ naloxone) film	buprenorphine/ naloxone sublingual tablets	Suboxone (buprenorphine/ naloxone) Film	Zubsolv (buprenorphine/ naloxone) sublingual tablets
Treatment of opioid dependence			✔		✔	✔
Treatment of opioid dependence and is preferred for induction		✔				
Maintenance treatment of opioid dependence				✔		
Treatment of moderate to severe opioid use disorder*	✔					

*For use in patients who initiated treatment with a transmucosal buprenorphine-containing product, followed by dose adjustment for at least 7 days.
(*Prescribing information: buprenorphine sublingual tablets 2021, buprenorphine/naloxone sublingual tablets 2021, Bunavail 2021, Sublocade 2021, Suboxone film 2021, Zubsolv 2021*)

Table 4. FDA-Approved Indications for Naltrexone Agents Used in Opioid Dependence

Indication	naltrexone HCl tablets	Vivitrol (naltrexone HCl) injection
Blockade of the effects of exogenously administered opioids	✔	
Treatment of alcohol dependence	✔	✔
Prevention of relapse to opioid dependence following opioid detoxification		✔

(*Prescribing information: naltrexone tablets 2017, Vivitrol 2021*)

Table 5. FDA-Approved Indications for Other Agents Used in Opioid Dependence

Indication	Lucemyra (lofexidine) tablets
Mitigation of opioid withdrawal symptoms to facilitate abrupt opioid discontinuation	✔

(*Prescribing information: Lucemyra 2020*)

Table 6. FDA-Approved Indications for Naloxone Products

Indication	Kloxxado (naloxone HCl) nasal spray	naloxone HCl injection	Narcan (naloxone HCl) nasal spray
Emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or CNS depression			✔
Emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or CNS depression, for adult and pediatric patients	✔		
Complete or partial reversal of opioid depression, including respiratory depression, induced by natural and synthetic opioids, including propoxyphene, methadone, and certain mixed agonist-antagonist analgesics: nalbuphine, pentazocine, butorphanol, and cyclazocine.		✔	
Diagnosis of suspected or known acute opioid overdosage		✔	
Adjunctive agent to increase blood pressure in the management of septic shock		✔	

Abbreviations: CNS= central nervous system

(*Prescribing information: Kloxxado 2021, naloxone injection 2021, Narcan nasal spray 2020*)

Limitations of use

- Prescription of Narcan nasal spray 2 mg should be restricted to opioid-dependent patients expected to be at risk for severe opioid withdrawal in situations where there is a low risk for accidental or intentional opioid exposure by household contacts.
- Naloxone nasal spray (Narcan, Kloxxado) is not a substitute for emergency medical care.

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

Products for Treatment of Opioid Dependence

- Clinical trials have demonstrated that buprenorphine/naloxone is practical and safe for use in diverse community treatment settings including primary care offices (*Amass et al 2004, Fiellin et al 2014*).
- Studies have shown that in adult patients with opioid dependence, the percentage of opioid-negative urine tests was significantly higher for both buprenorphine and buprenorphine/naloxone compared to placebo, while no significant difference was seen between the 2 active treatment groups (*Daulouède et al 2010, Fudala et al 2003*). In addition, a small randomized controlled trial (n = 32) also showed no significant difference in withdrawal symptoms between buprenorphine and buprenorphine/naloxone (*Strain et al 2011*).
- Several studies have compared the effectiveness of short-term detoxification to medium- or long-term maintenance treatment with buprenorphine monotherapy or buprenorphine/naloxone. Three studies have shown higher treatment retention rates or lower self-reported drug use rates with longer treatment duration compared to detoxification; however, 1 of the studies showed no significant difference in the percentage of positive urine tests between the 2 treatment groups at 12 weeks (*Kakko et al 2003, Weiss et al 2011, Woody et al 2008*).
- In a meta-analysis of 21 randomized controlled trials, patients receiving buprenorphine at doses ≥ 16 mg/day were more likely to continue treatment compared to patients receiving doses < 16 mg/day; however, no significant difference was seen in the percentage of opioid-positive urine tests between the high- and low-dose groups (*Fareed et al 2012*).
- Studies that compared different dosing regimens of buprenorphine showed no difference in rate of treatment retention, percentage of urine tests positive for opioids, or withdrawal symptoms (*Bickel et al 1999, Gibson et al 2008, Petry et al 1999, Schottenfeld et al 2000*).
- One study found that buprenorphine/naloxone sublingual film was comparable to the sublingual tablet form in dose equivalence and clinical outcomes (*Lintzeris et al 2013*).

- A randomized, parallel-group, noninferiority trial (n = 758) found that for the treatment of patients with opioid dependence, Zubsolv (buprenorphine/naloxone) sublingual tablets was noninferior to generic buprenorphine sublingual tablets during induction and was noninferior to buprenorphine/naloxone sublingual film during early stabilization (*Gunderson et al 2015*).
- Buprenorphine has been compared to methadone in several clinical studies and reviewed in multiple meta-analyses. Most studies have demonstrated that buprenorphine-based therapy was as effective as methadone in the management of opioid dependence; however, some newer data suggest that buprenorphine may be superior in this regard (*Bahji et al 2019, Dalton et al 2019*, *Farré et al 2002, Gibson et al 2008, Gowing et al 2017, Johnson et al 1992, Kamien et al 2008, Law et al 2017, Meader 2010, Perry et al 2015, Petitjean et al 2001, Soyka et al 2008, Strain et al 2011).* In a 2019 meta-analysis (n = 150,235 patients across 32 cohort studies), overall mortality rates were higher with methadone vs buprenorphine; however, when comparing time in-treatment to time out-of-treatment, methadone significantly reduced mortality vs buprenorphine (*Bahji et al 2019*). In another meta-analysis that same year (n = 370,611 patients across 30 studies), buprenorphine demonstrated lower all-cause mortality post-medication assisted therapy (MAT) vs methadone or naltrexone. However, all-cause mortality during MAT was lowest with naltrexone, followed by buprenorphine and methadone (*Ma et al 2019*).
- A meta-analysis of 4 randomized controlled trials compared methadone versus buprenorphine (3 studies) or methadone versus slow-release morphine (1 study) in pregnant women with opioid-dependence *(Minozzi et al 2020).* Although the comparison of methadone versus buprenorphine was based on limited evidence, methadone and buprenorphine were generally found to be similar in safety and efficacy for pregnant women and their children based on available data.
- When low doses of buprenorphine were studied (≤ 8 mg/day), high doses of methadone (≥ 50 mg/day) proved to be more efficacious *(Farré et al 2002, Ling et al 1996, Mattick et al 2014, Schottenfeld et al 1997*).
- In another 2019 meta-analysis (n = 847 overdose events across 4 studies), there was no statistically significant difference for retention in treatment between patients who received buprenorphine/naloxone vs buprenorphine or methadone alone (*Dalton et al 2019*).
- In a 24-week, Phase 3, double-blind, placebo-controlled, randomized controlled trial (n = 504), the efficacy and safety of multiple SC injections of buprenorphine (100 mg and 300 mg) over 24 weeks were assessed in treatment-seeking patients with opioid use disorder. Buprenorphine injection was shown to be superior to placebo in achieving more illicit opioid-free weeks ($p < 0.0001$). The proportion of patients achieving treatment success (defined as any patient with at least 80% of urine samples negative for opioids combined with negative self-reports for illicit opioid use from week 5 through week 24) was statistically significantly higher in both groups receiving buprenorphine compared to the placebo group (28% [300 mg/100 mg], 29% [300 mg/300mg], and 2% [placebo]) ($p < 0.0001$) *(FDA Advisory Committee Briefing Document 2017, Haight et al 2019)*.
- Extended-release IM naltrexone was compared to buprenorphine/naloxone sublingual film in a 24-week, open-label, randomized controlled trial (n = 570). More induction failures were seen with extended-release IM naltrexone; as a result, in the intention-to-treat analysis, relapse-free survival was lower with extended-release IM naltrexone compared to sublingual buprenorphine/naloxone. However, among patients who were able to successfully initiate treatment, extended-release IM naltrexone had similar efficacy to buprenorphine/naloxone in terms of relapse prevention (*Lee et al 2018*). A longitudinal secondary analysis of this trial examined urine testing data for non-study opioids from the last 22 weeks of the 24-week trial. Investigators found that in the per protocol sample (n=474) of patients who took at least one dose of medication, patients who were taking buprenorphine/naloxone had significantly greater proportions of opioid-positive tests in 14 out of the 22 weeks, suggesting that extended-release naltrexone may offer benefit over buprenorphine/naloxone in reducing illicit opioid use during treatment in this sample. However, this difference was not noted in patients who completed (n=211) the entirety of treatment (*Mitchell et al 2021)*. A 12-week, randomized, open-label, noninferiority trial (n = 159) similarly found that extended-release IM naltrexone was noninferior to oral buprenorphine/naloxone in terms of negative urine drug tests and days of opioid use (*Tanum et al 2017).*
- In a meta-analysis examining the efficacy of oral naltrexone for maintenance treatment of opioid dependence, oral naltrexone was no better than placebo or any pharmacologic treatment in terms of treatment retention or use of the primary substance of abuse. Based on the results of 1 study, it was also not significantly different from buprenorphine for retention, abstinence, and side effects (*Minozzi et al 2011*). A small, randomized, open-label study (n = 60) found that patients receiving extended-release IM naltrexone were twice as likely to remain in treatment for 6 months compared to patients receiving oral naltrexone (*Sullivan et al 2019*).
- The safety and efficacy of lofexidine for inpatient treatment of opioid withdrawal symptoms was examined in an 8-day, randomized, double-blind, placebo-controlled trial (n = 264). In this study, patients treated with lofexidine had lower

scores on the Short Opioid Withdrawal Scale (SOWS) Gossop scale on day 3 compared to placebo. More patients in the placebo group terminated study participation early (*Gorodetzky et al 2017).* Similar results were found in another placebo-controlled trial *(Fishman et al 2019)*. Meta-analyses have found that although lofexidine reduces withdrawal symptoms compared to placebo, it is less effective than buprenorphine for managing opioid withdrawal in terms of withdrawal severity, withdrawal duration, and likelihood of treatment completion *(Gowing et al 2016, Gowing et al 2017)*. It is likely to be less effective than buprenorphine or methadone for opioid detoxification (*Meader 2010*).

Products for Emergency Treatment of Opioid Overdose

- The approval of Narcan nasal spray and Kloxxado nasal spray were based on pharmacokinetic bioequivalence studies comparing these products to a generic naloxone product, delivered SC or IM. No clinical studies were required by the FDA (*Prescribing information: Kloxxado 2021, Narcan 2020*).
  - The manufacturers also conducted a human factors validation study in which participants were asked to deliver a simulated dose of the drug to a mannequin without training and most demonstrated appropriate use of the device (*FDA Summary Review: Narcan nasal spray 2015*).
- Studies have suggested that IN naloxone is an effective option in the treatment of opioid overdose (*Kelly et al 2005, Kerr et al 2009, Merlin et al 2010, Robertson et al 2009, Sabzghabaee et al 2014*). However, results from a recent double-blind, double-dummy, randomized clinical trial found that IN naloxone may not reverse overdose as efficiently as IM naloxone, replicating findings from previous unblinded trials (*Dietze et al 2019*). Kloxxado nasal spray delivers 8 mg of naloxone, a higher dose than what is delivered by Narcan nasal spray, to treat opioid overdose (*Kloxxado Prescribing information 2021).* Future clinical trials are required to determine if this increased dose of IN naloxone impacts reversal compared to previous studies.
- A meta-analysis of naloxone studies found that lay administration of naloxone was associated with significantly increased odds of recovery compared with no naloxone administration (odds ratio, 8.58; 95% confidence interval [CI], 3.90 to 13.25) (*Giglio et al 2015*).
- A 2-year, non-randomized intervention study found that prescribing naloxone to patients who were prescribed long-term opioids for chronic pain was associated with a 47% decrease in opioid-related emergency visits per month after 6 months and a 63% decrease after 1 year compared to those who did not receive naloxone (*Coffin et al 2016*).
- A retrospective cohort study including 3,085 patients found that of out-of-hospital naloxone administration improved outcomes for approximately 73% of patients with presumed opioid overdose (*Ashburn et al 2020*).

CLINICAL GUIDELINES

- The American Academy of Pediatrics (AAP), APA, ASAM, SAMHSA, and the Veterans Health Administration (VHA) have published guidelines for the treatment of opioid dependence. In general, these guidelines support access to all FDA-approved pharmacological therapies for the management of opioid dependence. Buprenorphine/naloxone combination products may be used for induction and maintenance. In pregnant women for whom buprenorphine therapy is selected, buprenorphine alone (ie, without naloxone) is recommended. Naltrexone may be considered for the prevention of relapse, although outcomes with this medication are often adversely affected by poor adherence. Extended-release injectable naltrexone may reduce, but not eliminate, some of the problems with oral naltrexone adherence. The VHA guideline recommends extended-release injectable naltrexone if opioid agonist treatment is not feasible. (*CSUP 2016, Cunningham et al 2020, Kampman et al 2015, Kleber et al 2006, SAMHSA treatment improvement protocol 2021, VHA 2015*).
- Updated 2020 clinical practice guidelines from ASAM recommend against opioid withdrawal management on its own (ie, detoxification) due to the associated high risk of relapse and other safety concerns; treatment with ongoing maintenance medication therapy in combination with psychosocial treatment as appropriate is the standard of care for opioid use disorder *(Cunningham et al 2020).*
  - The ASAM specifically recommends using methadone or buprenorphine for opioid withdrawal management over abrupt cessation of opioids.
  - Opioid withdrawal management with buprenorphine should not be initiated until objective signs of opioid withdrawal are present.
  - Alpha-2 adrenergic agonists (eg, lofexidine and clonidine) are safe and effective for withdrawal management; however, methadone and buprenorphine are more effective in reducing withdrawal symptoms.

- Various organizations including the WHO and the ASAM have endorsed the availability of naloxone for patients, bystanders, and first responders for the emergency management of suspected opioid overdose. It is recommended that people who are likely to witness an overdose should have access to and be trained in the use of naloxone (*Cunningham et al 2020, WHO 2014*).
  - According to the WHO guidelines for community management of opioid overdose, naloxone is effective when delivered by IV, IM, SC, and IN routes of administration. Persons using naloxone should select a route of administration based on the formulation available, their skills in administration, the setting, and local context.

SAFETY SUMMARY

- In July 2020, the FDA issued a drug safety communication recommending that healthcare professionals discuss the availability of naloxone with all patients receiving opioid pain relievers and consider prescribing it for patients who are at high risk or have a close contact at risk of overdose or accidental ingestion (*FDA Drug Safety Communication 2020*).

Products for Treatment of Opioid Dependence

- Buprenorphine and buprenorphine/naloxone products are contraindicated in patients with known hypersensitivity to the active ingredients.
  - Buprenorphine products have several warnings and precautions, including abuse potential; respiratory depression; CNS depression; unintentional pediatric exposure; neonatal opioid withdrawal; adrenal insufficiency; risk of opioid withdrawal with abrupt discontinuation of treatment; hepatitis and hepatic events; hypersensitivity reactions; precipitation of opioid withdrawal signs and symptoms; use in patients with impaired hepatic function; impairment of ability to drive or operate machinery; orthostatic hypotension; elevation of cerebrospinal fluid pressure; elevation of intracholedochal pressure; and effects in acute abdominal conditions. It is strongly recommended to prescribe naloxone at the same time as buprenorphine (if not dispensing a combination buprenorphine/naloxone product) due to the potential for relapse and opioid overdose.
  - Concomitant use of buprenorphine with benzodiazepines or other CNS depressants increases the risk for adverse events, including overdose, respiratory depression, and death. Cessation of benzodiazepines or other CNS depressants is preferred in most cases of concomitant use. This additional warning was added to opioid products in February 2018 after data demonstrated an increased risk of mortality in patients receiving benzodiazepines while on opioid maintenance treatment (*Abrahamsson et al 2017, FDA Drug Safety Communication 2017*).
  - The buprenorphine SC injection also has several unique warnings and precautions, including serious harm or death if administered IV (boxed warning); risks associated with treatment of emergent acute pain; and use in patients at risk for arrhythmia.
  - In the treatment of addiction involving opioid use in pregnant women, the buprenorphine/naloxone combination product is not recommended for use (insufficient evidence); however, the buprenorphine monoproduct is a reasonable and recommended option for use.
  - Similar to other opiate products, these products may increase intracholedochal pressure, increase cerebrospinal fluid pressure, and obscure diagnosis or exacerbate acute abdominal symptoms.
  - These products should not be used as analgesics.
  - The most common adverse reactions observed with buprenorphine and buprenorphine/naloxone products include headache, insomnia, nausea, pain, sweating, and withdrawal syndrome.
  - All of the buprenorphine-containing products have an associated risk evaluation and mitigation strategy (REMS) program (*REMS@FDA 2021*).
- Lofexidine has several warnings and precautions, including risk of hypotension, bradycardia, and syncope; risk of QT prolongation; increased risk of CNS depression with concomitant use of CNS depressant drugs; and increased risk of opioid overdose in patients who complete opioid discontinuation and resume opioid use.
  - Sudden discontinuation of lofexidine can cause a marked rise in blood pressure and symptoms that include diarrhea, insomnia, anxiety, chills, hyperhidrosis, and extremity pain. Lofexidine should be discontinued by gradually reducing the dose.
  - The most common adverse reactions observed with lofexidine include orthostatic hypotension, bradycardia, hypotension, dizziness, somnolence, sedation, and dry mouth.
  - The safety of lofexidine in pregnancy has not been established.
- Naltrexone products are contraindicated in patients receiving opioid analgesics; patients currently dependent on opioids (including those currently maintained on opioid agonists); patients in acute opioid withdrawal; individuals who have failed

a naloxone challenge test or have a positive urine screen for opioids; individuals with a history of sensitivity to naltrexone or other components of the product; and individuals with acute hepatitis or liver failure (oral naltrexone only). Extended-release injectable naltrexone is contraindicated in patients with hypersensitivity to polylactide-co-glycolide (PLG), carboxymethylcellulose, or any other component of the diluent.

- Naltrexone can precipitate withdrawal if given to an opioid-dependent patient. Prior to initiating naltrexone, an opioid-free interval of 7 to 10 days is recommended for patients previously dependent on short-acting opioids; patients transitioning from buprenorphine or methadone may be vulnerable to precipitation of withdrawal symptoms for up to 2 weeks. A naloxone challenge test may be helpful to determine whether or not the patient has had a sufficient opioid-free period prior to initiating naltrexone.
- Patients may be more vulnerable to opioid overdose after discontinuation of naltrexone due to decreased opioid tolerance.
- Monitor patients on naltrexone for the development of depression or suicidality.
- Warnings unique to extended-release IM naltrexone include injection site reactions, which may be severe; eosinophilic pneumonia; hypersensitivity reactions, including anaphylaxis; use in patients with thrombocytopenia or any coagulation disorder; and interference with certain immunoassay methods of urine opioid detection.
- The most common adverse reactions observed with oral naltrexone include difficulty sleeping, anxiety, nervousness, abdominal pain/cramps, nausea/vomiting, low energy, joint and muscle pain, and headache. The most common adverse reactions observed with extended-release IM naltrexone include hepatic enzyme abnormalities, injection site pain, nasopharyngitis, insomnia, and toothache.
- There are no adequate and well-controlled studies of naltrexone in pregnant women; it should be used only if the potential benefit justifies the potential risk to the fetus.
- Extended-release IM naltrexone has a REMS program due to the risk of severe injection site reactions (*REMS@FDA 2021*).

Products for Emergency Treatment of Opioid Overdose

- These products are contraindicated in patients with hypersensitivity to naloxone or to any of the other ingredients.
- These products carry warnings and precautions for risks of recurrent respiratory and CNS depression, limited efficacy with partial agonists or mixed agonists/antagonists (eg, buprenorphine, pentazocine), and precipitation of severe opioid withdrawal, and increased risk of adverse cardiovascular events.
- Naloxone may precipitate acute withdrawal symptoms in opioid-dependent patients including anxiety, tachycardia, sweating, piloerection, yawning, sneezing, rhinorrhea, nausea, vomiting, diarrhea, increased blood pressure, and abdominal or muscle cramps. Opioid withdrawal signs and symptoms in neonates also include convulsions, excessive crying, and hyperactive reflexes.

DOSING AND ADMINISTRATION

Table 7a. Dosing and Administration for Products for Treatment of Opioid Dependence

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Single Entity Agents				
buprenorphine	Sublingual tablets	Oral	Single daily dose	• Severe hepatic impairment: Consider reducing the starting and titration incremental dose by half and monitor for signs and symptoms of toxicity or overdose
Lucemyra (lofexidine)	Tablet	Oral	Four times daily at 5- to 6-hour intervals	• May be continued for up to 14 days with dosing guided by symptoms • Adjust dose for patients with hepatic or renal impairment

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
naltrexone hydrochloride	Tablet	Oral	Single daily dose May also be dosed every other day or every 3 days	• Contraindicated in patients with acute hepatitis or liver failure • Use caution in patients with hepatic or renal impairment
Sublocade (buprenorphine)	SC injection	SC	Monthly (minimum 26 days between doses) May be instances where a 2-month dosing interval is appropriate	• Can only be administered by a healthcare provider • Patients with moderate or severe hepatic impairment are not candidates for this product
Vivitrol (naltrexone extended-release)	IM injection	IM	Monthly or every 4 weeks	• Can only be administered by a healthcare provider • Use caution in patients with moderate to severe renal impairment
Combination Products				
Bunavail, Suboxone, Zubsolv (buprenorphine/ naloxone)	Buccal film (Bunavail) Sublingual film (Suboxone) Sublingual tablet (Zubsolv; generics equivalent to Suboxone tablet)	Oral	Bunavail: Single daily dose (except day 1 of induction for patients dependent on heroin or other short-acting opioid products: start with an initial dose of 2.1 mg/0.3 mg and repeat at approximately 2 hours, under supervision, to a total dose of 4.2 mg/0.7 mg based on the control of acute withdrawal symptoms) Suboxone: Single daily dose (except day 1 of induction: titrate in buprenorphine 2 mg to 4 mg increments at approximately 2-hour intervals based on the control of acute symptoms) Sublingual tablet generics (Suboxone): Single daily dose Zubsolv: Single daily dose (except day 1 of induction: divided into doses of 1 to 2 tablets of 1.4 mg/0.36 mg at 1.5 to 2-hour intervals)	• These products should generally be avoided in patients with severe hepatic impairment and may not be appropriate for patients with moderate hepatic impairment.

See the current prescribing information for full details

Table 7b. Equivalent Doses of Buprenorphine/Naloxone Combination Products*

buprenorphine/naloxone sublingual tablets and/or Suboxone sublingual film	Zubsolv sublingual tablets
2 mg/0.5 mg	1.4 mg/0.36 mg
4 mg/1 mg	2.9 mg/0.71 mg
8 mg/2 mg	5.7 mg/1.4 mg
12 mg/3 mg	8.6 mg/2.1 mg
16 mg/4 mg	11.4 mg/2.9 mg

*Systemic exposures of buprenorphine and naloxone may differ when patients are switched from tablets to films or vice versa.

Table 8. Dosing and Administration for Products for Emergency Treatment of Opioid Overdose

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Kloxxado (naloxone HCl)	Nasal spray	IN	A single spray should be administered into 1 nostril Additional doses should be administered, using a new nasal spray device in alternating nostrils, if the patient does not respond or responds and then relapses into respiratory depression. Additional doses may be given every 2 to 3 minutes until emergency medical assistance arrives.	Kloxxado delivers a single dose of 8 mg of naloxone HCl Additional supportive and/or resuscitative measures may be helpful while awaiting emergency medical assistance
naloxone HCl	Vials, prefilled syringe, solution cartridge	IV	*Adults:* An initial dose may be administered IV. It may be repeated at 2 to 3-minute intervals if the desired degree of counteraction and improvement in respiratory functions are not obtained. *Children:* The usual initial dose in children is given IV; a subsequent dose may be administered if the desired degree of clinical improvement is not obtained.	IM or SC administration may be necessary if the IV route is not available.
Narcan (naloxone HCl)	Nasal spray	IN	A single spray should be administered into 1 nostril. Additional doses should be administered, using a new nasal spray device in alternating nostrils, if the patient does not respond or responds and then relapses into respiratory depression. Additional doses may be given every 2 to 3 minutes until emergency medical assistance arrives.	Narcan delivers single doses of 2 mg or 4 mg naloxone HCl Additional supportive and/or resuscitative measures may be helpful while awaiting emergency medical assistance

See the current prescribing information for full details

CONCLUSION

Products for Treatment of Opioid Dependence

- Buprenorphine sublingual tablets, buprenorphine/naloxone sublingual tablets, Bunavail (buprenorphine/naloxone) buccal film, Sublocade (buprenorphine) SC injection, Suboxone (buprenorphine/naloxone) sublingual film, and Zubsolv (buprenorphine/naloxone) sublingual tablets are used for the treatment of opioid dependence. Some products are indicated for maintenance treatment only, while others are indicated for both induction and maintenance.
- Buprenorphine is suggested as a first-line maintenance treatment for moderate-to-severe opioid use disorder; it may be preferred over methadone because it is safer and does not require clinic-based treatment. Buprenorphine is typically administered in a combination product with naloxone, an opioid antagonist, to discourage abuse. These agents are Schedule III controlled substances (*Strain 2021*).
- Clinical trials have demonstrated that buprenorphine/naloxone is practical and safe for use in diverse community treatment settings including primary care offices (*Amass et al 2004, Fiellin et al 2014*).
- Physicians prescribing buprenorphine for opioid dependency must undergo specialized training due to the potential for abuse and diversion. Because of these risks, buprenorphine monotherapy should be reserved for patients who are pregnant or have a documented allergy to naloxone (*DATA 2000*).
- Most studies have demonstrated that buprenorphine-based therapy was as effective as methadone in the management of opioid dependence; however, some newer data suggest that buprenorphine may be superior in this regard (*Bahji et al 2019, Dalton et al 2019, Farré et al 2002, Gibson et al 2008, Gowing et al 2017, Johnson et al 1992, Kamien et al 2008, Meader 2010, Petitjean et al 2001, Soyka et al 2008, Mattick et al 2014, Strain et al 2011*).
- The most common adverse reactions observed with buprenorphine and buprenorphine/naloxone products include headache, insomnia, nausea, pain, sweating, and withdrawal syndrome. These products also have REMS criteria.
- Lofexidine is an oral central alpha-2 agonist indicated for mitigation of opioid withdrawal symptoms to facilitate abrupt opioid discontinuation.
- Meta-analyses have found that although lofexidine reduces withdrawal symptoms compared to placebo, it is less effective than buprenorphine for managing opioid withdrawal in terms of withdrawal severity, withdrawal duration, and likelihood of treatment completion *(Gowing et al 2016, Gowing et al 2017)*. It is likely to be less effective than buprenorphine or methadone for opioid detoxification (*Meader 2010*).
- The most common adverse reactions observed with lofexidine include orthostatic hypotension, bradycardia, hypotension, dizziness, somnolence, sedation, and dry mouth.
- Naltrexone is an opioid antagonist. Oral naltrexone is indicated for the treatment of alcohol dependence and blockade of the effects of exogenously administered opioids. Extended-release IM naltrexone is indicated for the treatment of alcohol dependence and the prevention of relapse to opioid dependence following opioid detoxification. In order to initiate naltrexone treatment, patients must be opioid-free for at least 7 to 10 days to avoid precipitation of withdrawal.
- In a meta-analysis examining the efficacy of oral naltrexone for maintenance treatment of opioid dependence, oral naltrexone was no better than placebo or any pharmacologic treatment in terms of treatment retention or use of the primary substance of abuse. Based on the results of 1 study, it was also not significantly different from buprenorphine for retention, abstinence, and side effects (*Minozzi et al 2011*). Extended-release IM naltrexone has been shown to have similar efficacy to oral buprenorphine/naloxone among patients who are able to successfully initiate treatment (*Lee et al 2018, Tanum et al 2017*). Retention rates with extended-release IM naltrexone are better than those seen with oral naltrexone (*Sullivan et al 2019*).
- The most common adverse reactions observed with oral naltrexone include difficulty sleeping, anxiety, nervousness, abdominal pain/cramps, nausea/vomiting, low energy, joint and muscle pain, and headache. The most common adverse reactions observed with extended-release IM naltrexone include hepatic enzyme abnormalities, injection site pain, nasopharyngitis, insomnia, and toothache. Extended-release IM naltrexone also has a REMS program.
- The AAP, APA, ASAM, SAMHSA, and VHA publish guidelines for the treatment of opioid dependence. These guidelines support access to all FDA-approved pharmacological therapies for the management of opioid dependence. Buprenorphine/naloxone combination products may be used for induction and maintenance. In pregnant women for whom buprenorphine therapy is selected, buprenorphine alone (ie, without naloxone) is recommended. Naltrexone may be considered for the prevention of relapse, although outcomes with this medication are often adversely affected by poor adherence. Extended-release injectable naltrexone may reduce, but not eliminate, some of the problems with oral naltrexone adherence. The VHA guideline recommends extended-release injectable naltrexone if opioid agonist

treatment is not feasible; it does not recommend for or against oral naltrexone (*CSUP 2016, Cunningham et al 2020, Kampman et al 2015, Kleber et al 2006, SAMHSA treatment improvement protocol 2021, VHA 2015).*

- Updated 2020 clinical practice guidelines from ASAM recommend against opioid withdrawal management on its own (ie, detoxification) due to the associated high risk of relapse and other safety concerns; treatment with ongoing maintenance medication therapy in combination with psychosocial treatment as appropriate is the standard of care for opioid use disorder *(Cunningham et al 2020).*
  - The ASAM specifically recommends using methadone or buprenorphine for opioid withdrawal management over abrupt cessation of opioids.
  - Opioid withdrawal management with buprenorphine should not be initiated until objective signs of opioid withdrawal are present.
  - Alpha-2 adrenergic agonists (eg, lofexidine and clonidine) are safe and effective for withdrawal management; however, methadone and buprenorphine are more effective in reducing withdrawal symptoms.

Products for Emergency Treatment of Opioid Overdose

- Naloxone is the standard of care to treat opioid overdose. It has been used by medical personnel for over 40 years and its use outside of the medical setting has gained traction through improvements in legislation and community-based opioid overdose prevention programs.
- Naloxone HCl injection, Kloxxado (naloxone HCl) nasal spray, and Narcan (naloxone HCl) nasal spray are approved for treatment of known or suspected opioid overdose. Prior to the approval of Narcan nasal spray, naloxone was only available in glass vials and ampules, which were distributed with syringes and needles for manual injection or with syringes and atomizers for off-label IN administration.
  - Naloxone injection can be administered IV, IM, or SC. Potential advantages of IN administration of naloxone include easier disposal, no needle stick risk, and avoidance of needle anxiety. Kloxxado nasal spray and Narcan nasal spray are designed for use by laypersons.
- The approvals of Kloxxado nasal spray and Narcan nasal spray were based on pharmacokinetic bioequivalence studies. No new clinical studies were required by the FDA. Kloxxado nasal spray, the most recently approved dosage form of naloxone, delivers 8 mg of naloxone, a higher dose than what is delivered by Narcan nasal spray, to treat opioid overdose.
- Various organizations including WHO and ASAM have endorsed the availability of naloxone for patients, bystanders, and first responders for the emergency management of suspected opioid overdose. It is recommended that people who are likely to witness an overdose should have access to and be trained in the use of naloxone (*WHO 2014, Cunningham et al 2020*).
  - According to the WHO guidelines for community management of opioid overdose, naloxone is effective when delivered by IV, IM, SC, and IN routes of administration. Persons using naloxone should select a route of administration based on the formulation available, their skills in administration, the setting, and local context.
- The U.S. HHS has recommended prescribing or co-prescribing naloxone to all patients who are at risk for opioid overdose, including: patients receiving opioids at a dosage of 50 MME per day or greater; patients with respiratory conditions who are prescribed opioids; patients who have been prescribed benzodiazepines along with opioids; and patients prescribed opioids who have a non-opioid substance use disorder, report excessive alcohol use, or have a mental health disorder (*HHS 2018*).

REFERENCES

- Abrahamsson T, Berge J, Ojehagen A, Hakansson A. Benzodiazepine, z-drug and pregabalin prescriptions and mortality among patients in opioid maintenance treatment-A nation-wide register-based open cohort study. *Drug Alcohol Depend*. 2017;174:58-64.
- Amass L, Ling W, Freese TE, et al. Bringing buprenorphine-naloxone to community treatment providers: the NIDA clinical trials network field experience. *Am J Addict*. 2004;13 Suppl 1:S42-66.
- American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. Fifth Ed. Arlington, VA: American Psychiatric Association; 2013:541-546.
- American Society of Addiction Medicine. Opioid Addiction 2016 Facts & Figures. http://www.asam.org/docs/default-source/advocacy/opioid-addiction-disease-facts-figures.pdf. Accessed August 4, 2021
- Ashburn NP, Ryder CW, Angi RM, et al. One-year mortality and associated factors in patients receiving out-of-hospital naloxone for presumed opioid overdose. *Ann Emerg Med*. 2020;75(5):559-567.
- Bahji A, Cheng B, Gray S, Stuart H. Reduction in mortality risk with opioid agonist therapy: a systematic review and meta-analysis. *Acta Psychiatr Scand;* 2019:140(4):313–339.

- Bickel WK, Amass L, Crean JP, Badger GJ. Buprenorphine dosing every 1, 2, or 3 days in opioid-dependent patients. *Psychopharmacology (Berl).* 1999;146(2):111-118.
- Bunavail. Prescribing information. Biodelivery Sciences International, Inc. March 2021.
- Buprenorphine and naloxone tablet. Prescribing information. Lannett Company, Inc. June 2021.
- Buprenorphine. Prescribing information. Sun Pharmaceutical Industries, Inc. Cranbury, NJ. April 2021.
- Centers for Disease Control and Prevention (CDC). Community-based opioid overdose prevention programs providing naloxone - United States, 2010. *MMWR Morb Mortal Wkly Rep*. 2012;61(6):101-105.
- Centers for Disease Control and Prevention (CDC). Opioid overdose. Updated July 15, 2021. Accessed August 4, 2021. https://www.cdc.gov/opioids/basics/index.html.
- Coffin P. Prevention of lethal opioid overdose in the community. UpToDate Web site. Updated May 18, 2021. Accessed August 4, 2021. https://www.uptodate.com/contents/prevention-of-lethal-opioid-overdose-in-the-community.
- Coffin PO, Behar E, Rowe C, et al. Nonrandomized intervention study of naloxone coprescription for primary care patients receiving long-term opioid therapy for pain. *Ann Intern Med.* 2016;165(4):245-252.
- Committee on Substance Use and Prevention (CSUP). Medication-Assisted Treatment of Adolescents With Opioid Use Disorders. *Pediatrics*. 2016;138(3):e20161893.
- Cunningham C, Edlund MJ, Fishman M, et al. The ASAM national practice guideline for the treatment of opioid use disorder: focused update. *J Addict Med*. 2020;14(2S Suppl 1):1-91.
- Dalton K, Butt N. Does the addition of naloxone in buprenorphine/naloxone affect retention in treatment in opioid replacement therapy?: a systematic review and meta-analysis. *J Addict Nurs*. 2019;30(4):254-260.
- Daulouède JP, Caer Y, Galland P, et al. Preference for buprenorphine/naloxone and buprenorphine among patients receiving buprenorphine maintenance therapy in France: a prospective, multicenter study. *J Subst Abuse Treat*. 2010;38(1):83-89.
- Dietze P, Jauncey M, Salmon A, et al. Effect of intranasal vs intramuscular naloxone on opioid overdose: a clinical trial. *JAMA Netw Open*. 2019;2(11):e1914977.
- Doe-Simkins M, Quinn E, Xuan Z, et al. Overdose rescues by trained and untrained participants and change in opioid use among substance-using participants in overdose education and naloxone distribution programs: a retrospective cohort study. *BMC Public Health*. 2014;14:297.
- Drugs@FDA: FDA approved drug products. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed August 10, 2021
- Fareed A, Vayalapalli S, Casarella J, Drexler K. Effect of buprenorphine dose on treatment outcome. *J Addict Dis*. 2012;31(1):8-18.
- Farré M, Mas A, Torrens M, Moreno V, Camí J. Retention rate and illicit opioid use during methadone maintenance interventions: a meta-analysis. *Drug Alcohol Depend*. 2002;65:283-290.
- FDA Drug Safety Communication: FDA recommends health care professionals discuss naloxone with all patients when prescribing opioid pain relievers or medicines to treat opioid use disorder. US Food & Drug Administration. July 23, 2020. https://www.fda.gov/drugs/drug-safety-and-availability/fda-recommends-health-care-professionals-discuss-naloxone-all-patients-when-prescribing-opioid-pain. Accessed August 10, 2021.
- FDA Drug Safety Communication: FDA urges caution about withholding opioid addiction medications from patients taking benzodiazepines or CNS depressants: careful medication management can reduce risks. US Food & Drug Administration. Updated September 26, 2017. https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-urges-caution-about-withholding-opioid-addiction-medications. Accessed August 10, 2021.
- FDA: Joint Meeting of Psychopharmacologic Drug Advisory Committee and Drug Safety and Risk Management Advisory Committee. Sublocade FDA Briefing Document. October 31, 2017. https://www.fda.gov/media/108382/download. Accessed August 10, 2021.
- Fiellin DA, Schottenfeld RS, Cutter CJ, et al. Primary-care based buprenorphine taper vs maintenance therapy for prescription opioid dependence: a randomized clinical trial. *JAMA Intern Med*. 2014;174(12):1947-1954.
- Fishman M, Tirado C, Alam D, et al. Safety and efficacy of lofexidine for medically managed opioid withdrawal: a randomized controlled clinical trial. J Addict Med. 2019;13(3):169-176.
- Fudala PJ, Bridge TP, Herbert S, et al. Office-based treatment of opiate addiction with a sublingual-tablet formulation of buprenorphine and naloxone. *N Engl J Med*. 2003;349(10):949-958.
- Gibson A, Degemhardt L, Mattick RP, et al. Exposure to opioid maintenance treatment reduces long term mortality. *Addiction.* 2008; 103(3):462-468.
- Giglio RE, Li G, DiMaggio CJ. Effectiveness of bystander naloxone administration and overdose education programs: a meta-analysis. *Inj Epidemiol*. 2015;2(1):10.
- Gorodetzky CW, Walsh SL, Martin PR, Saxon AJ, Gullo KL, Biswas K. A phase III, randomized, multi-center, double blind, placebo controlled study of safety and efficacy of lofexidine for relief of symptoms in individuals undergoing inpatient opioid withdrawal. *Drug Alcohol Depend*. 2017;176:79-88.
- Gowing L, Farrell M, Ali R, White JM. Alpha$_2$-adrenergic agonists for the management of opioid withdrawal. *Cochrane Database Syst Rev*. 2016;(5):CD002024.
- Gowing L, Ali R, White JM, Mbewe D. Buprenorphine for the management of opioid withdrawal. *Cochrane Database Syst Rev*. 2017;2:CD002025.
- Gunderson EW, Hjelmström P, Sumner M; 006 Study Investigators. Effects of a higher-bioavailability buprenorphine/naloxone sublingual tablet versus buprenorphine/naloxone film for the treatment of opioid dependence during induction and stabilization: a multicenter, randomized trial. *Clin Ther*. 2015;37(10):2244-2255.
- Haight BR, Learned SM, Laffont CM, et al. Efficacy and safety of a monthly buprenorphine depot injection for opioid use disorder: a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2019;393(10173):778-790.
- Johnson RE, Jaffe JH, Fudala PJ. A controlled trial of buprenorphine treatment for opioid dependence. *JAMA*. 1992;267(20):2750–2755.
- Kakko J, Svanborg KD, Kreek MJ, Heilig M. One-year retention and social function after buprenorphine-assisted relapse prevention treatment for heroin dependence in Sweden: a randomized, placebo-controlled trial. *Lancet*. 2003;361(9358):662-668.
- Kamien J, Branstetter S, Amass L. Buprenorphine-naloxone vs methadone maintenance therapy: a randomized double-blind trial with opioid-dependent patients. *Heroin Addict Relat Clin Probl*. 2008;10:5-18.
- 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):358-67.

- Kelly AM, Derr D, Dietze P, et al. Randomised trial of intranasal versus intramuscular naloxone in prehospital treatment for suspected opioid overdose. *MJA*. 2005; 182:24-27.
- Kerr D, Kelly AM, Dietze P, et al. Randomized controlled trial comparing the effectiveness and safety of intranasal and intramuscular naloxone for the treatment of suspected heroin overdose. *Addiction.* 2009;104:2067-2074.
- Kleber HD, Weiss RD, Anton RF, et al. for the American Psychiatric Association Workgroup on Substance Use Disorders, Treatment of patients with substance use disorders, second edition. American Psychiatric Association. *Am J Psychiatry*. 2006;163(8 Suppl):5-82.
- Kloxxado. Prescribing information. Hikma Pharmaceuticals USA, Inc. April 2021.
- Law FD, Diaper AM, Melichar JK, Coulton S, Nutt DJ, Myles JS. Buprenorphine/naloxone versus methadone and lofexidine in community stabilisation and detoxification: A randomised controlled trial of low dose short-term opiate-dependent individuals. *J Psychopharmacol*. 2017;31(8):1046-1055.
- 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(10118):309-318.
- Lexicomp Web site. http://online.lexi.com/lco/action/home. Accessed August 10, 2021
- Ling W, Wesson D, Charuvastra C, Klett CJ. A controlled trial comparing buprenorphine and methadone maintenance in opioid dependence. *Arch Gen Psychiatry*. 1996;53:401-407.
- Lintzeris N, Leung SY, Dunlop AJ, et al. A randomized controlled trial of sublingual buprenorphine-naloxone film versus tablets in the management of opioid dependence. *Drug Alcohol Depend*. 2013;131:119-126.
- Lucemyra. Prescribing information. US WorldMeds, LLC. September 2020.
- Ma J, Bao Y, Wang R, et al. Effects of medication-assisted treatment on mortality among opioids users: a systematic review and meta-analysis. *Mol Psychiatry*. 2019;24(12):1868-1883.
- Mattick RP, Breen C, Kimber J, Davoli M. Buprenorphine maintenance vs placebo or methadone maintenance for opioid dependence. *Cochrane Database Syst Rev.* 2014;2:CD002207.
- Meader N. A comparison of methadone, buprenorphine and alpha(2) adrenergic agonists for opioid detoxification: a mixed treatment comparison meta-analysis. *Drug Alcohol Depend*. 2010;108(1-2):110-114.
- Merlin MA, Saybolt M, Kapitanyan R, et al. Intranasal naloxone delivery is an alternative to intravenous naloxone for opioid overdoses. *Am J Emerg Med*. 2010;28(3):296-303.
- Micromedex®. IBM Corporation. 2021. Accessed August 10, 2021. http://www.micromedexsolutions.com/home/dispatch.
- Minozzi S, Amato L, Jahanfar S, Bellisario C, Ferri M, Davoli M. Maintenance agonist treatments for opiate-dependent pregnant women. *Cochrane Database Syst Rev.* 2020;11:CD006318.
- Minozzi S, Amato L, Vecchi S, Davoli M, Kirchmayer U, Verster A. Oral naltrexone maintenance treatment for opioid dependence. *Cochrane Database Syst Rev.* 2011;(4):CD001333.
- Mitchell MM, Schwartz RP, Choo TH, et al. An alternative analysis of illicit opioid use during treatment in a randomized trial of extended-release naltrexone versus buprenorphine-naloxone: A per-protocol and completers analysis. *Drug Alcohol Depend.* 2021;219:108422.
- Naloxone HCl. Prescribing information. Mylan Institutional LLC. April 2021.
- Naltrexone tablet. Prescribing information. SpecGx LLC. July 2017.
- Narcan Nasal Spray FDA Summary Review. Drugs@FDA Web site. November 18, 2015. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/208411Orig1s000SumR.pdf. Accessed August 10, 2021.
- Narcan nasal spray. Prescribing information. Emergent Devices, Inc. November 2020.
- Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations. US Food & Drug Administration, Center for Drug Evaluation and Research. http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed August 10, 2021.
- Perry AE, Neilson M, Martyn-St James M, et al. Pharmacological interventions for drug-using offenders. *Cochrane Database Syst Rev.* 2015;6: CD010862. doi: 10.1002/14651858.CD010862.pub2.
- Petitjean S, Stohler R, Deglon J, et al. Double-blind randomized trial of buprenorphine and methadone in opiate dependence. *Drug Alcohol Depend.* 2001;62:97-104.
- Petry NM, Bickel WK, Badger GJ. A comparison of four buprenorphine dosing regimens in the treatment of opioid dependence. *Clin Pharmacol Ther*. 1999;66(3):306-314.
- REMS@FDA. US Food & Drug Administration, Center for Drug Evaluation and Research. 2021. http://www.accessdata.fda.gov/scripts/cder/rems/. Accessed August 10, 2021.
- Robertson TM, Hendey GW, Stroh G, Shalit M. Intranasal naloxone is a viable alternative to intravenous naloxone for prehospital narcotic overdose. *Prehosp Emerg Care.* 2009;13(4):512-515.
- Sabzghabaee AM, Eizadi-Mood N, Yaraghi A, Zandifar S. Naloxone therapy in opioid overdose patients: intranasal or intravenous? A randomized clinical trial. *Arch Med Sci.* 2014;10(2):309-314.
- SAMHSA Opioid Overdose Prevention Toolkit. HHS Publication No. (SMA) 18-4742. Substance Abuse and Mental Health Services Administration Web site. June 2018. https://store.samhsa.gov/system/files/sma18-4742.pdf. Accessed August 10, 2021
- SAMHSA. Statutes, regulations, and guidelines. Substance Abuse and Mental Health Services Administration Web site. Updated June 24, 2021. https://www.samhsa.gov/medication-assisted-treatment/statutes-regulations-guidelines. Accessed August 10, 2021
- SAMHSA. Treatment Improvement Protocol (TIP) 63: Medications for opioid use disorder. Substance Abuse and Mental Health Services Administration Web site. https://store.samhsa.gov/product/TIP-63-Medications-for-Opioid-Use-Disorder-Full-Document/PEP20-02-01-006. Updated July 2021. Accessed August 10, 2021.
- Schottenfeld R, Pakes J, Oliveto A, Ziedonis D, Kosten TR. Buprenorphine vs methadone maintenance treatment for concurrent opioid dependence and cocaine abuse. *Arch Gen Psychiatry*. 1997;54:713-720.
- Schottenfeld RS, Pakes J, O'Connor P, et al. Thrice-weekly vs daily buprenorphine maintenance. *Biol Psychiatry*. 2000;47(12):1072-1079.
- Soyka M, Zingg C, Koller G, Kuefner H. Retention rate and substance use in methadone and buprenorphine maintenance therapy and predictors of outcome: results from a randomized study. *Int J Neuropsychopharmacol*. 2008;11:641-653.
- Strain E. Pharmacotherapy for opioid use disorder. UpToDate Web site. https://www.uptodate.com. Updated July 28, 2021. Accessed August 10, 2021.

- Strain EC, Harrison JA, Bigelow GE. Induction of opioid-dependent individuals onto buprenorphine and buprenorphine/naloxone soluble-films. *Clin Pharmacol Ther*. 2011;89(3):443-449.
- Sublocade. Prescribing information. Indivior, Inc. June 2021.
- Suboxone film. Prescribing information. Indivior, Inc. March 2021.
- 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(2):129-137. doi: 10.1176/appi.ajp.2018.17070732.
- 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(12):1197-1205. doi: 10.1001/jamapsychiatry.2017.3206.
- US Department of Health & Human Services (HHS). Naloxone: the opioid reversal drug that saves lives. December 2018. https://www.hhs.gov/opioids/sites/default/files/2018-12/naloxone-coprescribing-guidance.pdf. Accessed August 10, 2021.
- Veterans Health Administration, Department of Defense. VA/DoD clinical practice guideline for the management of substance use disorders (SUD). Washington (DC): Veterans Health Administration, Department of Defense; 2015. http://www.healthquality.va.gov/Substance_Use_Disorder_SUD.asp. Accessed August 10, 2021.
- Vivitrol. Prescribing information. Alkermes, Inc. March 2021.
- Weiss RD, Potter JS, Fiellin DA, et al. Adjunctive counseling during brief and extended buprenorphine-naloxone treatment for prescription opioid dependence: a two-phase randomized controlled trial. *Arch Gen Psychiatry*. 2011;68(12):1238-1246.
- Woody GE, Poole SA, Subramaniam G, et al. Extended vs short-term buprenorphine-naloxone for treatment of opioid-addicted youth: a randomized trial. JAMA. 2008;300(17):2003-2011.
- World Health Organization: Community management of opioid overdose. World Health Organization Web site. https://www.who.int/publications/i/item/9789241548816. Updated November 2, 2014. Accessed September 23, 2021.
- Zubsolv. Prescribing information. Orexo US, Inc. March 2021.

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