



Opiate Dependence Treatments Therapeutic Class Review (TCR)

December 20, 2019

No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopying, recording, digital scanning, or via any information storage or retrieval system without the express written consent of Magellan Rx Management.

All requests for permission should be mailed to:

Magellan Rx Management
Attention: Legal Department
6950 Columbia Gateway Drive
Columbia, Maryland 21046

The materials contained herein represent the opinions of the collective authors and editors and should not be construed to be the official representation of any professional organization or group, any state Pharmacy and Therapeutics committee, any state Medicaid Agency, or any other clinical committee. This material is not intended to be relied upon as medical advice for specific medical cases and nothing contained herein should be relied upon by any patient, medical professional or layperson seeking information about a specific course of treatment for a specific medical condition. All readers of this material are responsible for independently obtaining medical advice and guidance from their own physician and/or other medical professional in regard to the best course of treatment for their specific medical condition. This publication, inclusive of all forms contained herein, is intended to be educational in nature and is intended to be used for informational purposes only. Send comments and suggestions to PSTCReDitor@magellanhealth.com.

December 2019

Proprietary Information. Restricted Access – Do not disseminate or copy without approval.
© 2004-2019 Magellan Rx Management. All Rights Reserved.

MagellanRx
MANAGEMENTSM

FDA-APPROVED INDICATIONS

Drug	Manufacturer	Indication
buprenorphine sublingual tablets ^{1,2}	generic	<ul style="list-style-type: none"> ▪ Treatment of opioid dependence (preferred for induction only); should be used as part of a complete treatment plan to include counseling and psychosocial support
buprenorphine extended-release injection (Sublocade™) ³	Indivior	<ul style="list-style-type: none"> ▪ 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; should be used as part of a complete treatment plan that includes counseling and psychosocial support
buprenorphine implant (subdermal) (Probuphine®) ^{4*}	Titan	<ul style="list-style-type: none"> ▪ Maintenance treatment of opioid dependence in patients who have achieved and sustained prolonged clinical stability on low-to-moderate doses of a transmucosal buprenorphine containing product (e.g., doses of no more than 8 mg per day of Subutex or Suboxone sublingual tablet or generic equivalent); should be used as part of a complete treatment plan to include counseling and psychosocial support
buprenorphine/naloxone buccal film (Bunavail®) ⁵	BioDelivery Sciences International	<ul style="list-style-type: none"> ▪ Treatment of opioid dependence (induction and maintenance); should be used as part of a complete treatment plan to include counseling and psychosocial support
buprenorphine/naloxone sublingual film (Suboxone®) ⁶	generic, Indivior	<ul style="list-style-type: none"> ▪ Treatment of opioid dependence (induction and maintenance); should be used as part of a complete treatment plan to include counseling and psychosocial support
buprenorphine/naloxone sublingual tablets (Zubsolv®) ⁷	Orexo	<ul style="list-style-type: none"> ▪ Treatment of opioid dependence (induction and maintenance); should be used as part of a complete treatment plan to include counseling and psychosocial support
buprenorphine/naloxone sublingual tablets ⁸	generic	<ul style="list-style-type: none"> ▪ Maintenance treatment of opioid dependence; should be used as part of a complete treatment plan to include counseling and psychosocial support
lofexidine (Lucemyra™) ⁹	US WorldMeds	<ul style="list-style-type: none"> ▪ Reduction of opioid withdrawal symptoms in adults following abrupt discontinuation of opioids
naloxone hydrochloride injection† (Evzio®) ¹⁰	Kaleo	<ul style="list-style-type: none"> ▪ Emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression; it is intended for immediate administration as emergency therapy in settings where opioids may be present
naloxone hydrochloride nasal spray‡ (Narcan®) ¹¹	Adapt	<ul style="list-style-type: none"> ▪ Emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression; it is intended for immediate administration as emergency therapy in settings where opioids may be present

* Buprenorphine implant (Probuphine) is not appropriate for new treatment entrants or patients without prolonged clinical stability while on low-to-moderate doses of a transmucosal buprenorphine-containing product for 3 months or longer.

† Generic naloxone solution for injection is available in vials of 0.4 mg/mL from multiple manufacturers.

‡ Limitation of use: naloxone (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.

FDA Approved Indications (continued)

Drug	Manufacturer	Indication
naltrexone hydrochloride tablets ¹²	generic	<ul style="list-style-type: none">▪ Treatment of opioid dependence▪ Treatment of alcohol dependence▪ Naltrexone has not shown to provide any therapeutic benefit except as part of an appropriate plan of management for the addictions
naltrexone extended-release injectable suspension (Vivitrol®) ¹³	Alkermes	<ul style="list-style-type: none">▪ Prevention of relapse to opioid dependence, following opioid detoxification▪ Treatment of alcohol dependence in patients who are able to abstain from alcohol in an outpatient setting▪ Naltrexone ER injection should be part of a comprehensive management program that includes psychosocial support

OVERVIEW

Prescription and illicit opioid abuse and misuse has reached national interest and was declared a National Public Health Emergency by the Department of Health and Human Services (DHHS) Acting Secretary in 2017.¹⁴ The 2018 National Survey on Drug Use and Health (NSDUH) reported there was an estimated 31.9 million Americans aged 12 years and older who were current (past month) illicit drug users.¹⁵ There were approximately 10.3 million people aged 12 or older in the United States (US) who misused opioids in the past year. Approximately 20.3 million people aged 12 or older in 2018 were considered to have a substance use disorder (SUD) in the past year, including 14.8 million people with an alcohol use disorder, 8.1 million people with an illicit drug use disorder, and 2 million had an opioid use disorder.

Methadone, a Schedule II controlled substance under the Controlled Substances Act (CSA), is a full opioid receptor agonist that has been thoroughly studied and is widely used as treatment for opioid dependence. It is orally active, can be dosed once daily, and can suppress symptoms of opioid withdrawal while blocking the effects of other opioids. Maintenance on methadone is generally safe. The most common adverse effects of methadone include constipation, sexual dysfunction, and sweating. Methadone users are also subject to effects of long-acting opioids like respiratory depression. A formal evaluation of methadone is not within the scope of this review.

Buprenorphine is a Schedule III controlled substance under the CSA and has the same potential for abuse as other opioids. Both buprenorphine and buprenorphine/naloxone can be used for office-based detoxification from opioids and maintenance treatment for opioid dependency by specially trained and registered physicians. Like methadone, buprenorphine can suppress opioid withdrawal symptoms and block the effects of other opioids. The American Psychiatric Association (APA) 2006 guidelines on the treatment of patients with substance abuse disorders suggest that buprenorphine may be best suited for patients with mild to moderate levels of physical dependence.¹⁶ In 2016, an implantable buprenorphine product (Probuphine) was approved. It offers an additional maintenance treatment option in patients stabilized on low-to-moderate doses of a transmucosal buprenorphine-containing product for a minimum of 3 months.¹⁷ An extended-release buprenorphine injection (Sublocade) was approved in 2017 to treat moderate to severe opioid use disorder in patients who have had a minimum of 7 days of transmucosal buprenorphine. This provides an additional option for maintenance therapy as part of a comprehensive treatment program.¹⁸ A Cochrane review of medications to manage opioid

withdrawal found no statistical difference between methadone and buprenorphine in treatment duration or treatment completion rates; however, published data are too limited to state conclusively that there are no differences in a clinical setting, and the withdrawal pattern or symptoms may differ slightly between treatments.¹⁹

Under the Drug Addiction Treatment Act of 2000 (DATA), in order to become a qualified practitioner, physicians must be licensed under State law to practice medicine, obtain a waiver from the US Substance Abuse and Mental Health Services Administration (SAMHSA), and notify the Secretary of the DHHS of their intention of prescribing or dispensing buprenorphine. Such practitioners hold a modified Drug Enforcement Administration (DEA) registration, in which they are designated by a unique identifier and must include it on each prescription written.^{20,21} Prescribers are limited in the number of patients they may treat under a waiver, but they may request approval to treat additional patients. In 2016, the DHHS increased this patient limit to 275 patients.²² The Substance Use Disorder Prevention that Promotes Opioid Recovery and Treatment for Patients and Communities Act extends the prescribing authority for medication-assisted treatment (MAT) to clinical nurse specialists, certified nurse midwives, and certified nurse anesthetists for 5 years and physician assistants and nurse practitioners indefinitely.²³ Qualified prescribers may immediately treat 100 patients if the prescriber is board certified in addiction medicine or addiction psychiatry or provides MAT in a qualified practice setting.

Oral naltrexone was approved in 1984 for the adjuvant treatment of patients dependent on opiate agonists. FDA approval of naltrexone for the treatment of alcoholism was granted in 1995.²⁴ The FDA approved Vivitrol, a once-monthly intramuscular naltrexone formulation for alcohol dependence in 2006, and then in 2010, Vivitrol was approved for the prevention of relapse to opioid dependence after opioid detoxification.

Naloxone hydrochloride injection has been utilized in the treatment for the complete or partial reversal of opioids and in the treatment of known or suspected opioid overdose (intravenous, subcutaneous and intramuscular routes of administration). The emergency treatment was primarily administered in clinics or hospital settings and by some first responders. Naloxone hydrochloride injection (Evzio) offers a unique delivery device with a pre-filled auto-injector (subcutaneous/intramuscular) and electronic voice instructor for emergency use, while awaiting emergency medical assistance. Naloxone nasal spray (Narcan) is also indicated for use for emergency treatment of opioid overdose in settings where opioids may be present. The nasal formulation offers an alternative to the naloxone auto-injector for treatment outside of healthcare settings. However, neither of these formulations should be considered substitutes for emergency medical care.

SAMHSA provides information on MAT, including training courses for buprenorphine use and opioid prescribing courses.²⁵ They also provide guides for medication-assisted treatment of opioid use disorder that highlight contraindications, warnings, and other concerns and briefly address who ideal candidates would be for each medication; they do not state that any one medication is appropriate over another for all patients. The SAMHSA website provides additional information on medication-assisted treatment for providers and patients. Many of these resources are available to guide prescribers as they select a treatment option for both the induction and maintenance phases as well as assist in navigating the legal requirements related to the use of these medications where needed.

The American Society of Addiction Medicine (ASAM) has published guidelines for the use of medications in the treatment of addiction involving opioid use.²⁶ These guidelines, adopted in 2015,

discuss treatment options and provide recommendations for medications during both the withdrawal and maintenance phases. They state that the choice of medication (e.g., buprenorphine, methadone, naltrexone) should be a shared decision between the clinician and patient and should consider patient preferences, treatment history, and treatment setting. Notably, they state buprenorphine may not be appropriate for patients with an active alcohol disorder or sedative-drug disorder. Likewise, methadone is recommended for patients who may benefit from additional supervision. Finally, oral naltrexone requires special attention to medication adherence and may require observed administration for some patients. Buprenorphine and methadone are the standard treatment options for managing the acute withdrawal from opioids. Other options included in the ASAM guidelines for acute opioid withdrawal are alpha₂ adrenergic agonists, such as clonidine and lofexidine. Despite significant clinical trial experience with clonidine, lofexidine (Lucemyra) is the only FDA-approved non-opioid treatment for the management of opioid withdrawal symptoms. Acute symptoms are typically managed in an inpatient setting for close monitoring. Alpha₂ adrenergic agonists are often used in combination with other agents to target multiple withdrawal symptoms. Following the acute withdrawal period, there is no consensus on the ideal duration of maintenance therapy, despite the availability of multiple guidelines and resources for the initiation and management of medications for opioid dependency.²⁷ In 2017, ASAM adopted guidance on the appropriateness of drug testing to guide clinicians in the clinical setting and emphasizes that the frequency and duration of testing should be individualized.²⁸

The World Health Organization (WHO) has published guidelines on the identification and management of substance use disorders in pregnancy.²⁹ They state pregnant women should be encouraged to use opioid maintenance treatment whenever available rather than attempt opioid detoxification (strong recommendation, very low quality of evidence) and patients should be advised to either continue or initiate treatment with buprenorphine or methadone (strong recommendation, very low quality of evidence).

In 2016, the Centers for Disease Control and Prevention (CDC) released guidelines for prescribing opioids for chronic pain outside of active cancer, palliative, and end-of-life care.³⁰ These guidelines are intended to encourage appropriate opioid use and help curb the opioid epidemic. The CDC includes 12 recommendations: 3 regarding when to initiate or continue opioids for chronic pain; 4 regarding opioid selection, dosage, duration, follow-up, and discontinuation; and 5 regarding assessing risk and addressing harms of opioid abuse. Regarding medications for opioid dependence, the CDC states prescribers should offer treatment for opioid use disorder (e.g., medication-assisted treatment, such as buprenorphine or methadone, in combination with behavioral therapies). Buprenorphine and methadone may be used in pregnant patients, but they state that oral or long-acting injectable formulations should be reserved for nonpregnant adults and those who are highly motivated. The CDC released an updated statement in 2019 regarding the intent of the 2016 guidelines to advise primary care providers treating adults with certain types of chronic pain.³¹ The recommendations emphasize the careful tapering of opioids to avoid withdrawal symptoms in current pain patients and individualized assessment of risks and benefits for continued high-dose treatment.

In response to the opioid abuse epidemic, in April 2016, the FDA announced plans to reassess their approach to opioid medications with a focus on policies to reverse the epidemic of deaths associated with opioid use. Plans include the use of an expert advisory committee prior to the approval of an opioid without abuse-deterrent properties, the formation of a Pediatric Advisory Committee who will review pediatric labeling for new products, an update of Risk Evaluation and Mitigation Strategies

(REMS) requirements, and improvement in access to abuse-deterrent formulations, naloxone, and other treatment options for patients with opioid-use disorders.³² In addition to the CDC and FDA advisory committees focus on the opioid epidemic, the FDA has also awarded a contract to the National Academies of Sciences, Engineering, and Medicine (NASEM) to develop evidence-based guidelines for opioid prescribing in specific acute pain conditions.³³ The goal of this program is to decrease inappropriate opioid prescribing that may lead to excess opioid supply and inappropriate exposure while maintaining access to adequate pain control for patients.

Expanded access to naloxone has also been a focus in curbing the opioid epidemic. The WHO recommends that people likely to witness an opioid overdose should have access to naloxone for emergency management (strong recommendation, very low quality of evidence).³⁴ The Surgeon General of the United States Public Health Service issued an advisory to support access to naloxone for patients, health care practitioners, family and friends, and community members who may come into contact with patients on prescription high-dose opioids, illicit heroin or fentanyl, or patients with opioid use disorder.³⁵ In December 2018, the US Department of Health and Human Services (DHHS) expanded upon this by releasing a statement recommending clinicians co-prescribe naloxone to patients prescribed an opioid who are at risk of opioid overdose.³⁶ This includes patients receiving ≥ 50 morphine milligram equivalents (MME) per day, with respiratory illness, receiving a benzodiazepine, or with a concomitant non-opioid substance use disorder (e.g., alcohol). Naloxone should also be prescribed to individuals at a high risk of experiencing or responding to an opioid overdose, such as a family member or friend of a person with an opioid use disorder, including those who have decreased opioid tolerance (e.g., after release from incarceration or other controlled setting).

PHARMACOLOGY^{37,38,39,40,41,42,43,44,45,46,47,48,49}

Buprenorphine is a partial agonist at the mu-opioid receptor and an antagonist at the kappa-opioid receptor. It is postulated that patients receiving buprenorphine are likely to experience euthymia due to the partial agonist activity at the mu-opioid receptor and antagonist activity at the kappa-opioid receptor. Buprenorphine effects may be limited by a ceiling effect.

Naloxone is an antagonist at the mu-opioid receptor. Buprenorphine/naloxone was co-formulated in order to prevent patients from abusing buprenorphine in combination with other opioids.

Naltrexone is an opioid antagonist with highest affinity for the mu opioid receptor. Naltrexone has few, if any, intrinsic actions besides its opioid blocking properties. However, it does produce some pupillary constriction, by an unknown mechanism. Naltrexone blocks the effects of opioids by competitive binding at opioid receptors. This makes the blockade produced potentially surmountable, but overcoming full naltrexone blockade by administration of opioids may result in non-opioid receptor-mediated symptoms, such as histamine release.

Lofexidine (Lucemyra) is a central alpha-2 agonist that reduces the release of norepinephrine and decreases sympathetic tone when it binds to adrenergic neurons. Lofexidine targets the symptoms of opioid withdrawal caused by noradrenergic hyperactivity.

PHARMACOKINETICS^{50,51,52,53,54,55,56,57,58,59,60,61,62}

Drug	Bioavailability (%)	Protein Binding (%)	Half-Life (hours)	Metabolism (Active Metabolite)	Elimination (%)
buprenorphine	variable	96 (alpha, beta globulin)	24–48	N-dealkylation, glucuronidation (norbuprenorphine)	urine: 30 feces: 69
buprenorphine extended-release injection	low	96 (alpha, beta globulin)	43-60 days	N-dealkylation, glucuronidation (norbuprenorphine)	urine: 30 feces: 69
lofexidine	72	55	12	no active metabolites	primarily urine
naloxone	low 46.7*	45 (albumin)	5–6.25; 1.5–1.6 [†]	glucuronidation, N-dealkylation, reduction	primarily urine
naltrexone	variable 5–40	21–28	biphasic naltrexone: 4 6β-naltrexol: 13	6β-naltrexol	primarily urine
naltrexone extended-release injectable suspension	low	21	5–10 days	6β-naltrexol, is mediated by dihydrodiol dehydrogenase	primarily urine

*Dose normalized relative bioavailability of a single 4 mg nasal spray compared to a 0.4 mg intramuscular injection

† Includes both 0.4 mg and 2 mg doses of naloxone (Evzio) in healthy adults

Peak buprenorphine plasma concentrations occur 12 hours after insertion of the buprenorphine extended-release implant (Probuphine); steady-state is reached in about 4 weeks and maintained for approximately 20 weeks. After buprenorphine extended-release injection (Sublocade) administration, peak plasma concentration occurs at 24 hours; steady-state is achieved at 4 to 6 months with repeated dosing.

Although the pharmacokinetics of buprenorphine/naloxone tablets and film are similar, not all doses and dose combinations met bioequivalence criteria.

The exposure of buprenorphine from 1 Bunavail 4.2/0.7 mg buccal film was equivalent to 1 Suboxone 8/2 mg sublingual tablet. The naloxone exposure from Bunavail buccal film was 33% less than with Suboxone sublingual tablets.

The exposure of 1 buprenorphine/naloxone (Zubsolv) 5.7/1.4mg tablet provides equivalent buprenorphine exposure and 12% lower naloxone exposure when compared to 1 buprenorphine/naloxone (generic; Suboxone) 8/2 mg tablet.

Four buprenorphine implants within 1 Probuphine implant system deliver comparable drug levels to that of ≤ 8 mg/day of buprenorphine (Subutex or Suboxone).

CONTRAINDICATIONS/WARNINGS^{63,64,65,66,67,68,69,70,71,72,73,74,75}

Buprenorphine (Probuphine, Sublocade) and buprenorphine/naloxone (Bunavail/Suboxone/Zubsolv) are contraindicated in patients who have been shown to be hypersensitive to buprenorphine. Buprenorphine/naloxone (Evzio) and naloxone (Narcan) are also contraindicated in patients who are hypersensitive to naloxone.

Buprenorphine implant (Probuphine) carries a boxed warning for implant migration, protrusion, expulsion, and nerve damage associated with insertion and removal; it is only available through the Probuphine Risk Evaluation and Mitigation Strategy (REMS) program described below.

Buprenorphine extended-release injection (Sublocade) carries a boxed warning for serious harm or death if the injection is administered intravenously. The injection forms a solid mass once it contacts body fluids and life threatening emboli could form if administered intravenously. Buprenorphine extended-release injection is only available through the Sublocade Risk Evaluation and Mitigation Strategy (REMS) program described below.

Patients receiving buprenorphine in the presence of other narcotic analgesics, general anesthetics, benzodiazepines, phenothiazines, other tranquilizers, sedative/hypnotics, or other central nervous system (CNS) depressants (including alcohol) may exhibit increased CNS depression. Significant respiratory depression or death has been associated with buprenorphine, particularly by the intravenous route, when taken with benzodiazepines or other CNS depressants. Buprenorphine or buprenorphine/naloxone should be used with caution in patients with compromised respiratory function (e.g., chronic obstructive pulmonary disease, cor pulmonale, decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression). Buprenorphine-containing medications should be kept out of reach of children as buprenorphine can cause severe or fatal respiratory depression in exposed pediatric patients. Despite this risk, the FDA advises that opioid addiction medications should not be withheld from patients who are also taking benzodiazepines or other CNS depressants.⁷⁶ The decision to use these medications concurrently should be used with caution and in consideration of the risks to the patient and under close supervision. Patient education, medication tapering, verifying medical necessity, and coordinating care may be required.

Buprenorphine, as with other opioids, may cause central sleep apnea (CSA) and sleep-related hypoxemia. Patients are at a higher risk for sleep-related breathing disorders as opioid doses increase. A safe opioid taper is recommended in patients who present with CSA.

Buprenorphine may impair the mental or physical abilities required for the performance of potentially dangerous tasks, such as driving a car or operating machinery, especially during drug induction and dose adjustment. Like other opioids, buprenorphine may produce orthostatic hypotension in ambulatory patients.

Buprenorphine, like other potent opioids, may elevate cerebrospinal fluid pressure and should be used with caution in patients with head injury, intracranial lesions, and other circumstances where cerebrospinal pressure may be increased.

Buprenorphine is a partial agonist at the mu-opiate receptor and chronic administration produces dependence of the opioid type, characterized by withdrawal upon abrupt discontinuation or rapid taper. Buprenorphine has the same abuse potential as other opioids. Therefore, prescribers should use caution when prescribing buprenorphine and consider its potential misuse, abuse, and diversion risk. Multiple refills should not take place in early therapy or without frequent patient follow-up visits.

Cases of cytolytic hepatitis and hepatitis with jaundice have been observed in the opiate-dependent population receiving buprenorphine both in clinical trials and in post-marketing adverse event reports. Measurement of liver function tests prior to initiation of treatment is recommended to establish a baseline. Periodic monitoring of liver function tests during treatment is also recommended. A dose adjustment is recommended in patients with severe hepatic impairment. Buprenorphine/naloxone products are not recommended in patients with severe hepatic impairment and may not be appropriate for patients with moderate hepatic impairment; individual components of a fixed-dose combination product cannot be individually titrated. Additional information is available in the Special Populations section below.

Like other opioids, buprenorphine-containing products have been shown to increase intracholedochal pressure and should be administered cautiously in patients with a dysfunctional biliary tract. Also like other opioids, buprenorphine may make diagnosis difficult or alter the clinical course of patients with acute abdominal conditions. Cases of adrenal insufficiency have been reported in association with greater than 1 month of opioid use. If diagnosis of adrenal insufficiency is confirmed, patients should be titrated off the opioid to allow the adrenal function to recover.

In clinical trials, buprenorphine has been observed to prolong the QTc interval in some patients. Additional, periodic electrocardiographic (ECG) monitoring is recommended in patients with hypokalemia, hypomagnesemia, or clinically unstable cardiac disease. Buprenorphine should be avoided in patients with a history of Long QT Syndrome or immediate family member with this history, concurrent use of a Class IA antiarrhythmic, Class III antiarrhythmic, or other medication that is known to prolong the QT interval.

Buprenorphine-containing products should be administered cautiously in the following patients: debilitated patients or patients with myxedema or hypothyroidism, adrenal cortical insufficiency, CNS depression or coma, toxic psychoses, prostatic hypertrophy or urethral stricture, acute alcoholism, delirium tremens, or hypophoscoliosis.

Deaths have occurred in opioid-naïve patients who received a 2 mg dose of buprenorphine sublingually for analgesia. Buprenorphine products in this review should not be used in opioid-naïve patients and are not appropriate for analgesia; however, other buprenorphine products (Belbuca® buccal film, Butrans® transdermal system, buprenorphine injection), which are not in the scope of this review, are approved to manage pain that requires daily, around-the-clock, long-term treatment for which alternative treatment options are inadequate. Due to the naloxone component, buprenorphine/naloxone is highly likely to produce marked and intense withdrawal symptoms if misused parenterally by individuals dependent on opiate agonists such as heroin, morphine, or methadone. Since buprenorphine is a partial agonist, it may precipitate opioid withdrawal effects if administered before the effects of a full agonist have subsided.

Neonatal opioid withdrawal syndrome (NOWS) has been reported in infants of women treated with buprenorphine containing products during pregnancy.

Naltrexone is contraindicated in patients currently taking opioids, in addition to any individual who has failed the naloxone challenge test or who has a positive urine screen for opioids. It is also contraindicated in patients with acute opioid withdrawal, physical dependence to opioids, liver disease, or a history of hypersensitivity reaction to naltrexone.

Naltrexone has the capacity to cause hepatocellular injury when given in excessive doses. Naltrexone is contraindicated in acute hepatitis or liver failure, and its use in patients with active liver disease must be carefully considered in light of its hepatotoxic effects. The margin of separation between the apparently safe dose of naltrexone and the dose causing hepatic injury appears to be only 5-fold or less. Naltrexone does not appear to be a hepatotoxin at the recommended doses. Patients should be warned of the risk of hepatic injury and advised to seek medical attention if they experience symptoms of acute hepatitis.

Patients should be under continued surveillance after administration of naloxone until emergency medical assistance arrives due to the short duration of action and possible requirement for administration of repeated doses. Other supportive and/or resuscitative actions may be useful until arrival of emergency medical assistance.

When administering naloxone, the reversal of respiratory depression by partial agonists or mixed agonists/antagonists, such as buprenorphine and pentazocine, may be incomplete; mechanical assistance may be required.

Patients with pre-existing cardiac disease or patients who may have received medications with possible adverse cardiovascular effects should be monitored in an appropriate healthcare setting after receiving naloxone.

As naloxone functions to reverse the effects of opioids, its use may precipitate severe withdrawal in opioid-dependent patients.

Lofexidine (Lucemyra) may cause a decrease in blood pressure, pulse, and syncope. Vital signs should be monitored before the dose of lofexidine, and ongoing monitoring for bradycardia, hypotension, and orthostasis is recommended. Due to the risk of cardiac side effects, lofexidine should be avoided in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease, chronic renal failure, or significant bradycardia.

Lofexidine is known to prolong the QT interval and should be avoided in patients with congenital long QT syndrome. A baseline ECG is recommended in patients with congestive heart failure, bradyarrhythmias, hepatic impairment, renal impairment, or patients taking other medications that prolong the QT interval.

Abrupt discontinuation of lofexidine may cause an increase in blood pressure in addition to diarrhea, insomnia, anxiety, chills, hyperhidrosis, and pain. Lofexidine should be tapered to avoid this response.

Lofexidine (Lucemyra) may potentiate the CNS depressive effects of alcohol, barbiturates, and other sedating drugs, including benzodiazepines. Patients should avoid driving or operating heavy machinery until response to lofexidine is known.

Patients who have discontinued opioids during initial treatment with lofexidine are at increased risk of fatal overdose if opioids are resumed. Patients diagnosed with opioid use disorder should use lofexidine in conjunction with a comprehensive management program.

Risk Evaluation and Mitigation Strategies (REMS)⁷⁷

There is a buprenorphine-containing transmucosal products for opioid dependence (BTOD) REMS that includes the following medications: buprenorphine tablets, buprenorphine/naloxone sublingual film and tablets, buprenorphine/naloxone sublingual tablets (Zubsolv), and buccal film (Bunavail). There is

also a shared REMS for Suboxone and Subutex branded products; however, only the Suboxone (buprenorphine/naloxone) film remains available and the branded tablets have been discontinued. Buprenorphine implant (Probuphine) also has its own REMS program. Each includes a medication guide, an implementation system, and elements to ensure safe use. Ultimately, the goal of these REMS is to mitigate the risk of overdose, abuse, and misuse. Other elements in place to ensure safe buprenorphine and buprenorphine/naloxone product use include verification of safe use conditions and patient monitoring. The buprenorphine implant has select requirements for both prescribers and for surgeons who implant or remove the insert to further ensure safety of use. Buprenorphine extended-release injection (Sublocade) has a REMS program to ensure the healthcare setting and pharmacy is certified and that the injection is dispensed directly from the pharmacy to a healthcare provider to avoid the risk of serious harm or death due to intravenous administration. The REMS program consists of enrollment by the wholesaler, healthcare setting, and pharmacy to control distribution and administration. Naltrexone ER injectable suspension (Vivitrol) also has a REMS program consisting of a medication guide and a communication plan.

DRUG INTERACTIONS^{78,79,80,81,82,83,84,85,86,87,88,89,90}

Buprenorphine is metabolized to norbuprenorphine by cytochrome CYP3A4. Because CYP3A4 inhibitors may increase plasma concentrations of buprenorphine, patients already on CYP3A4 inhibitors should be closely monitored and may require buprenorphine or buprenorphine/naloxone dose adjustments.

The interaction of buprenorphine with CYP3A4 inducers has not been studied; therefore, it is recommended that patients receiving buprenorphine be monitored for signs and symptoms of opiate withdrawal if inducers of CYP3A4 (e.g., efavirenz, phenobarbital, carbamazepine, phenytoin, rifampicin) are co-administered.

Lofexidine (Lucemyra) is metabolized by CYP2D6 and co-administration with a strong inhibitor, such as paroxetine, may result in orthostatic hypotension and bradycardia.

Patients receiving buprenorphine or lofexidine (Lucemyra) in the presence of other CNS depressants (including alcohol) may exhibit increased CNS depression. Caution should also be used in patients using both buprenorphine and agents impacting serotonin, including monoamine oxidase inhibitors (MAOIs), as cases of serotonin syndrome have been reported when serotonergic agents are used concurrently with opioids.

Buprenorphine has been observed to prolong the QTc interval in some patients and should be avoided in patients on concurrent use of a Class IA antiarrhythmic, Class III antiarrhythmic, or other medication that is known to prolong the QT interval. Patients receiving lofexidine with methadone should undergo routine ECG monitoring to assess for prolongation of the QT interval.

Like other opioids, buprenorphine may decrease the efficacy of diuretic medications by inducing the release of antidiuretic hormone. Patients should be monitored for effects on blood pressure and diminished diuresis if prescribed together.

Patients receiving concomitant anticholinergic medications and buprenorphine should be monitored for signs of urinary retention and reduced gastric motility. Severe constipation due to this combination of drugs may lead to paralytic ileus.

Post-marketing reports have indicated the combination of buprenorphine and benzodiazepines have resulted in coma and death. In many of these cases, buprenorphine was misused by self-injecting the medication. Physicians should use extreme caution if prescribing the medications together.

Patients taking non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PI) with buprenorphine should be monitored as dose adjustments of buprenorphine may be needed.

Patients taking naltrexone may not benefit from opioid-containing medicines. Because naltrexone is not a substrate for CYP drug metabolizing enzymes, inducers or inhibitors of these enzymes are unlikely to change the clearance of naltrexone. Naltrexone antagonizes the effects of opioid-containing medicines, such as cough and cold remedies, antidiarrheal preparations, and opioid analgesics. Concomitant use of disulfiram and oral naltrexone is recommended by manufacturers only if potential benefits justify the risk, as both drugs are potentially hepatotoxic.

In an open-label, single-arm study, co-administration of oral naltrexone with lofexidine (Lucemyra) resulted in reduced overall exposure of oral naltrexone if used within 2 hours of lofexidine (Lucemyra).

For alcohol dependence, the safety profile of patients treated with naltrexone concomitantly with antidepressants was similar to that of patients taking naltrexone without antidepressants.

ADVERSE EFFECTS^{91,92,93,94,95,96,97,98,99,100,101,102,103}

Drug	Headache	Abdominal Pain	Withdrawal Syndrome	Constipation	Nausea	Insomnia
buprenorphine	28 to 34 (22.4)	11.7 (6.5)	18.4 to 24 (37.4)	5 to 14 (2.8)	7 to 13.6 (11.2)	21.4 to 28 (15.9)
buprenorphine extended-release injection (Sublocade)*	8.5 to 9.4 (6)	nr	nr	8 to 9.4 (0)	8 to 8.9 (5)	nr
buprenorphine subdermal implant (Probuphine) [†]	> 5	nr	nr	> 5	> 5	nr
buprenorphine/naloxone SL film/tablet (Suboxone)	36.4 (22.4)	11.2 (6.5)	25.2 (37.4)	12.1 (2.8)	15 (11.2)	14 (15.9)
buprenorphine/naloxone SL tablet (Zubsolv) [‡]	7 (7)	reported	reported	reported	5 (6)	reported
buprenorphine/naloxone buccal film (Bunavail) [§]	≥ 5	nr	≥ 5	> 1 to < 5	nr	> 1 to < 5

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all inclusive. Incidences for the placebo group are indicated in parentheses.

* Adverse effects reported from 6-month clinical trial and include injection site reactions: site pain, pruritus, erythema, and induration.

[†] Adverse effects related to administration: site pain, pruritus and erythema.

[‡] Additional adverse effect data obtained from other formulations of buprenorphine or buprenorphine/naloxone.

[§] Data obtained from a 12-week open-label clinical study.

Adverse Effects (continued)

Drug	Headache	Abdominal Pain	Withdrawal Syndrome	Constipation	Nausea	Insomnia
lofexidine (Lucemyra)	nr	nr	nr	nr	nr	51 to 55 (48)
naloxone hydrochloride injection (Evzio)	nr	reported	reported	reported	reported	nr
naloxone hydrochloride nasal spray (Narcan)	reported	reported	reported	reported	reported	nr
naltrexone extended-release injectable suspension (Vivitrol)	3 (2)	nr**	nr	nr	reported	6 (1)
naltrexone hydrochloride	> 10	> 10	reported	< 10	> 10	> 10

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all inclusive. Incidences for the placebo group are indicated in parentheses.

^{||} Adverse effects also include experience with naloxone hydrochloride injection in healthcare settings.

^{**} Abdominal pain not reported for opioid dependence data but reported for alcohol dependence.

Abrupt reversal of opioid effects on those physically dependent on opioids may result in an acute withdrawal syndrome, resulting in the above noted adverse effects in the administration of naloxone hydrochloride injection. Abrupt reversal of opioid depression may also present in the following: nausea, vomiting, sweating, tachycardia, seizures, pulmonary edema, and cardiac arrest which may result in death. There is a risk for opioid withdrawal symptoms during the transition of patients from full opioid agonists to the partial opioid agonist, buprenorphine. The goal of the induction period with transmucosal buprenorphine is to avoid opioid withdrawal symptoms and to facilitate the transition when buprenorphine extended-release injection (Sublocade) is to be used.

Adverse events reported in at least 10% of patients treated with lofexidine (Lucemyra) and occurring in more patients than placebo include orthostatic hypotension, bradycardia, dizziness, somnolence, sedation, and dry mouth. Syncope (0.9% to 1.4%) and tinnitus (0.9% to 3.2%) were also reported more frequently in treated patients than patients exposed to placebo but did not reach the 10% threshold. Lofexidine (Lucemyra) is also associated with blood pressure elevations after discontinuation of treatment with a 5-day course. The blood pressure value peaked on the second day after discontinuation in the patients assessed in clinical trials.

In clinical trials, few differences in the adverse event profile were noted among Suboxone sublingual film, Zubsolv sublingual tablets, Bunavail buccal film, buprenorphine sublingual tablets, and a buprenorphine ethanolic sublingual solution. The most common adverse event (greater than 1%) associated with Suboxone sublingual film was oral hypoesthesia, which was not reported with sublingual tablet formulations. Other adverse events were glossodynia, oral mucosal erythema, intoxication, disturbance in attention, palpitations, and hyperhidrosis. When used for treatment of opioid dependence, the most common adverse effects of naltrexone extended-release injectable suspension were injection site reactions, hypertension, sleeplessness, toothache, inflammation of the nasopharynx, and liver enzyme changes. These occurred in at least 2% of patients. In patients receiving

buprenorphine (Probuphine), additional adverse effects reported (greater than 5%) included depression, oropharyngeal pain, toothache, and back pain. Administration related adverse reactions (greater than 10%) included site pain, pruritus and erythema.

Postmarketing cases of serotonin syndrome have been reported in patients using concomitant opioids, such as buprenorphine, and serotonergic drugs.

Cases of androgen deficiency have also been reported in patients with chronic opioid use. This is theorized to be related to the influence of opioids on the hypothalamic-pituitary-gonadal axis.

The following adverse reactions have been identified during use of naloxone hydrochloride in the post-operative setting: hypotension, hypertension, ventricular tachycardia and fibrillation, dyspnea, pulmonary edema, and cardiac arrest. Death, coma, and encephalopathy have been reported as sequelae of these events. Excessive doses of naloxone hydrochloride in post-operative patients have resulted in significant reversal of analgesia and have caused agitation. In addition, in some patients, there may be aggressive behavior upon abrupt reversal of an opioid overdose.

Additional adverse effects reported with naloxone hydrochloride (Narcan) nasal spray include hypertension, musculoskeletal pain, muscle spasms, headache, constipation, toothache, nasal dryness, nasal edema, nasal congestion, rhinalgia, xeroderma, and nasal inflammation.

SPECIAL POPULATIONS^{104,105,106,107,108,109,110,111,112,113,114,115,116}

Pediatrics

The safety and effectiveness of buprenorphine sublingual tablets, buprenorphine extended-release injection (Sublocade), or buprenorphine/naloxone (Bunavail/Suboxone) in pediatric patients have not been established. Safety and efficacy of buprenorphine (Probuphine) subdermal implant and buprenorphine/naloxone tablets (Zubsolv) have not been established in pediatric patients under the age of 16 years.

The safety and effectiveness of lofexidine (Lucemyra) have not been established in pediatric patients.

The safety and efficacy of naltrexone extended-release injectable suspension (Vivitrol), as well as naltrexone oral tablet have not been established in the pediatric population.

The safety and effectiveness of both naloxone hydrochloride formulations, Evzio auto-injector and Narcan nasal spray, have been established in pediatric patients for known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression.

Following subcutaneous or intramuscular administration of naloxone hydrochloride in pediatric patients, absorption may be erratic or delayed. Careful monitoring is required for at least 24 hours even when dramatic response is observed because relapse may occur as the drug is metabolized. Administration of naloxone may result in abrupt and complete reversal of opioid effects; therefore, pediatric patients must be monitored for acute opioid withdrawal syndrome. In neonates, this syndrome may be life-threatening and treatment should be according to protocols developed by experts in neonatology.

Neonates and pediatric patients less than 1 year of age should be observed at the administration site for evidence of residual needle parts and/or signs of infection following the administration of naloxone injection.

Pregnancy

Naltrexone tablets are Pregnancy Category C. All other products in this class have had the labeling replaced with descriptive information in accordance with the Pregnancy and Lactation Labeling Rule (PLLR). There is limited data with the use of naloxone in pregnant women and naloxone may precipitate withdrawal in the fetus. Likewise, there are no well-controlled studies of Probuphine in pregnant women. The safety of lofexidine (Lucemyra) in pregnant women has not been established. Abrupt discontinuation of opioid therapy in dependent, pregnant females is not recommended. While there are no well-controlled studies of buprenorphine sublingual tablets, limited published data on use of buprenorphine have not shown an increased risk of major fetal malformations when used by pregnant women. Patients should be monitored for signs of withdrawal during pregnancy and doses should be adjusted as needed. Also, additional analgesia may be needed during labor. Dosage adjustments may be needed during and after pregnancy.

Renal Impairment

When intravenous buprenorphine was administered to dialysis-dependent patients and normal patients, no difference in buprenorphine pharmacokinetics was observed. Clinical studies of buprenorphine extended-release injection (Sublocade) and buprenorphine implant (Probuphine) did not include patients with renal impairment.

Lofexidine (Lucemyra) dosage adjustments are recommended in patients with moderate and severe renal impairment due to a reduction in elimination. Dialysis does not remove lofexidine (Lucemyra); therefore, supplemental doses do not need to be considered in patients on dialysis.

The effects of naloxone in renal failure are unknown. Caution is recommended in administering oral naltrexone to patients with renal impairment. Caution is recommended in administering naltrexone extended-release injectable to patients with moderate to severe renal impairment.

Hepatic Impairment

Dosage should be adjusted in this population, with patients monitored for symptoms of opiate withdrawal. Naltrexone carries a boxed warning for causing hepatocellular injury when given in excessive doses and is contraindicated in acute hepatitis or liver failure. Use of naltrexone should be discontinued in the event of symptoms and/or signs of acute hepatitis.

Dose adjustment of naltrexone extended-release injectable (Vivitrol) is not required in mild to moderate hepatic impairment. Naltrexone extended-release injectable has not been evaluated in severe hepatic impairment.

Dose reductions of lofexidine (Lucemyra) are recommended in patients with hepatic impairment due to a decrease in elimination.

Plasma exposure and half-life have been found to be longer in patients with moderate to severe hepatic impairment; however, a dose adjustment of buprenorphine sublingual tablets is only recommended in patients with severe hepatic impairment.

Hepatic impairment has shown to result in a greater reduction in the clearance of naloxone than that of buprenorphine. Buprenorphine/naloxone fixed dose combinations prohibit individual titration of the products. Therefore, patients with severe hepatic impairment will encounter higher levels of naloxone than those with normal hepatic function. An increased risk of precipitated withdrawal may result in the

induction phase of treatment and may also interfere with the efficacy of buprenorphine throughout treatment. As a result, buprenorphine/naloxone products are not recommended in patients with severe hepatic impairment and may be inappropriate in patients with moderate hepatic impairment. Due to the possibility of naloxone interfering with the efficacy of buprenorphine, patients should be closely monitored for signs and symptoms of opioid withdrawal.

Patients with pre-existing moderate to severe hepatic impairment are not candidates for buprenorphine implant (Probuphine) or buprenorphine extended-release injection (Sublocade). Patients who develop hepatic impairment during treatment should be monitored for toxicity and overdose of buprenorphine. Removal of the implant may be required if signs of toxicity appear; removal of the depot may be required if signs appear within 2 weeks of administration.

Geriatrics

The safety and efficacy of buprenorphine, lofexidine, naloxone, or naltrexone have not been studied adequately to determine if an older population would respond differently than younger patients. Dose adjustments similar to those recommended for renal impairment should be considered in patients over 65 years of age when prescribed lofexidine. Prescribers should use caution when prescribing buprenorphine to older patients since they have greater frequency of decreased cardiac, hepatic, and renal function, have more concomitant diseases, and often take multiple drugs. Geriatric patients should be started at the lowest dose possible.

DOSAGES^{117,118,119,120,121,122,123,124,125,126,127,128,129}

Drug	Dosing	Availability
buprenorphine SL tablets	<p>For the treatment of opioid dependence induction:</p> <ul style="list-style-type: none"> – For patients dependent on short-acting opioid products or heroin in opioid withdrawal, the first dose should be administered when objective signs of moderate opioid withdrawal appear and not less than 4 hours after patient last used opioid – For patients dependent on long-acting opioid products and/or methadone, the first dose should be administered when objective signs of moderate opioid withdrawal appear and not less than 24 hours after the patient last used opioid – Adults and Adolescents ≥ 16 years: 8 mg buprenorphine sublingually on day 1, 16 mg buprenorphine sublingually on day 2, and then the patient should begin maintenance treatment; dosage titration over 2 days rather than 3 to 4 days appears to result in greater treatment success <p>For opioid dependence maintenance</p> <p>When used for maintenance dosing, adjustments should be made in increments or decrements of 2 to 4 mg to a dose that maintains a level of treatment which suppresses opioid withdrawal; the general range of buprenorphine maintenance dose is 4 mg to 24 mg per day; doses beyond this have not shown any clinical advantage; patients may require treatment indefinitely and should continue for as long as the patient continues to benefit</p>	2 mg, 8 mg sublingual tablets

Dosages (continued)

Drug	Dosing	Availability
buprenorphine extended-release injection (Sublocade)	<p>For the treatment of moderate to severe opioid use disorder in patients following induction and dose adjustment with a transmucosal buprenorphine-containing product for a minimum of 7 days:</p> <ul style="list-style-type: none"> – 300 mg SC injection monthly for 2 months followed by maintenance dosing of 100 mg SC injection monthly – The maintenance dose may be increased to 300 mg SC injection monthly for patients who tolerate the 100 mg injection but do not demonstrate a clinical response – No less than 26 days between doses <p>Injections are administered by a healthcare provider (HCP) into the subcutaneous tissue in the abdomen no more frequently than every 26 days - see package insert for specifics regarding administration procedure</p>	100 mg/0.5 mL, 300 mg/1.5 mL prefilled syringe with safety needle
buprenorphine implant, subdermal (Probuphine)	<p>For the maintenance treatment of opioid dependence in patients who have achieved and sustained prolonged clinical stability on low-to-moderate doses of a transmucosal buprenorphine-containing product: (see package insert for specifics regarding implantation procedure)</p> <ul style="list-style-type: none"> – 4 implants inserted subdermally by an HCP in the inner upper arm and retained in place for 6 months (remove by the end of 6 months; – insertion site should be evaluated 1 week after placement; visit schedule frequency should be no less than once-monthly for continued counseling and psychosocial support; if spontaneous expulsion occurs, patients should see provider promptly – If additional supplemental transmucosal buprenorphine doses are needed after implant is placed, patient should be seen and evaluated promptly; do not provide patients with as-needed buprenorphine-containing products; alternatives to the buprenorphine implant should be considered for patients requiring ongoing supplemental transmucosal buprenorphine during implant use – May repeat treatment for 1 additional treatment course (total of 12 months) by inserting a new set of 4 implants into opposite arm; if this cannot be done on the same day as removal, maintain treatment with previous transmucosal buprenorphine dosage following removal until new implants are placed; If additional treatment is needed following two, 6-month implants, transition patient back to transmucosal buprenorphine 	Implant kit: 4-sterile implants containing 74.2 mg (equivalent to 80 mg of buprenorphine HCl; 26 mm by 2.5 mm) and 1 disposable applicator

Dosages (continued)

Drug	Dosing	Availability
buprenorphine/naloxone buccal film (Bunavail)	<p>For the induction of opioid agonist dependence treatment:</p> <ul style="list-style-type: none"> – For patients dependent on short-acting opioid products or heroin in opioid withdrawal: <ul style="list-style-type: none"> ○ Day 1: initial dose of 2.1/0.3 mg, repeat in 2 hours (total up to 4.2/0.7 mg) ○ Day 2: up to 8.4/1.4 mg as a single dose – To avoid precipitating withdrawal syndrome, the first dose should be started when objective signs of moderate withdrawal appear (not less than 6 hours after the last used opioids) – For patients dependent on long-acting opioid products and/or methadone the recommended treatment is sublingual buprenorphine monotherapy due to the higher risk of precipitated and prolonged withdrawal; after induction, patients can then be transitioned to once daily Bunavail buccal film – Additional titration details are outlined in the prescribing information <p>For the maintenance treatment of opioid dependence in patients who have been initially inducted using buprenorphine sublingual tablets:</p> <ul style="list-style-type: none"> – From Day 3 onward; dose adjustments should be made in increments/decrements of 2.1/ 0.3 mg to a level that suppresses opioid withdrawal symptoms; recommended target daily dose: 8.4/1.4 mg daily (single dose) – Maintenance dose range: 2.1/0.3 mg to 12.6/2.1 mg daily; higher doses have not shown any clinical advantage; no more than 2 films should be applied to 1 cheek at a time; patients may require treatment indefinitely and should continue for as long as the patient continues to benefit – If the patient is switching from Suboxone sublingual tablets, the equivalency chart in the package insert should be followed; a Bunavail 4.2/0.7 mg buccal film provide equivalent exposure to a Suboxone 8/2 mg sublingual film 	2.1/0.3 mg, 4.2/0.7 mg, 6.3/1 mg buccal films (citrus flavor)

Dosages (continued)

Drug	Dosing	Availability
buprenorphine/naloxone SL film (Suboxone)	<p>For the induction of opioid agonist dependence treatment:</p> <ul style="list-style-type: none"> – For patients dependent on short-acting opioid products or heroin in opioid withdrawal: <ul style="list-style-type: none"> ○ Day 1: initial dose of 2/0.5 mg or 4/1 mg; may titrate upwards in 2 mg to 4 mg increments of buprenorphine, at 2 hour intervals to maximum of 8/2 mg ○ Day 2: up to 16/4 mg as a single dose – To avoid precipitating withdrawal syndrome, the first dose should be started when objective signs of moderate withdrawal appear; not less than 6 hours after the last used opioids – For patients dependent on long-acting opioid products and/or methadone: recommended treatment is sublingual buprenorphine monotherapy on Days 1 and 2; after induction, patients can then be transitioned to once daily sublingual film – Additional titration details are outlined in the prescribing information <p>For the maintenance treatment of opioid dependence:</p> <ul style="list-style-type: none"> – Titrate dosage in increments of 2–4 mg/day of buprenorphine to a dose that holds the patient in treatment and suppresses opioid withdrawal symptoms; doses above 24 mg/day have not shown any added benefit; an adequate maintenance dose, titrated to clinical effectiveness, should be achieved as rapidly as possible to avoid drop-out of patients during the induction period – Following induction to opioid dependence treatment, a target dose of 16/4 mg buprenorphine/naloxone sublingually once daily is suggested; however, doses ranging from 4 to 24 mg/day of the buprenorphine component may be required; patients may require treatment indefinitely and should continue for as long as the patient continues to benefit 	2/0.5 mg, 4/1 mg, 8/2 mg, 12/3 mg sublingual films

Dosages (continued)

Drug	Dosing	Availability
buprenorphine/ naloxone SL tablets (Zubsolv)	<p>For the induction of opioid agonist dependence treatment:</p> <ul style="list-style-type: none"> – For patients dependent on heroin or other short-acting opioid products: <ul style="list-style-type: none"> ○ Day 1: initiate with 1.4/0.36 mg, repeat at 1.5 to 2 hour intervals for a total daily dose up to 5.7/1.4 mg ○ Day 2: single dose up to 11.4/2.9 mg is recommended – May be induced on buprenorphine/naloxone SL tablets or with sublingual buprenorphine monotherapy; the dose should be initiated when moderate signs of opioid withdrawal appear (not less than 6 hours after the patient last used opioids) – For patients dependent on long-acting opioid products and/or methadone: recommended treatment is sublingual buprenorphine monotherapy on Days 1 and 2; after induction, patients can then be transitioned to once daily sublingual tablet – Additional titration details are outlined in the prescribing information <p>For the maintenance of opioid agonist dependence treatment:</p> <ul style="list-style-type: none"> – Titrate dose in increments of 1.4/0.36 mg or 2.9/0.71 mg of buprenorphine/naloxone to a dose that holds the patient in treatment and suppresses opioid withdrawal symptoms; doses above 17.2/4.2 mg per day of buprenorphine/naloxone have not shown to provide any additional clinical benefit – Following induction to opioid dependence treatment, a target dose of 11.4/2.9 mg buprenorphine/naloxone is recommended; however, doses ranging from 2.9/0.71 mg buprenorphine/naloxone to 17.2/4.2 mg buprenorphine/naloxone may be required; patients may require treatment indefinitely and should continue for as long as the patient continues to benefit 	0.7/0.18 mg, 1.4/0.36 mg, 2.9/0.71 mg, 5.7/1.4 mg, 8.6/2.1 mg, 11.4/2.9 mg sublingual tablets
buprenorphine/ naloxone SL tablets	<p>For the maintenance of opioid agonist dependence treatment:</p> <ul style="list-style-type: none"> – Titrate dose in increments of 2/0.5 mg/day or 4/1 mg/day of buprenorphine/naloxone to a dose that holds the patient in treatment and suppresses opioid withdrawal symptoms; doses above 24/6 mg per day of buprenorphine/naloxone have not shown to provide additional clinical benefit – Following induction to opioid dependence treatment, a target dose of 16/4 mg buprenorphine/naloxone is recommended; however, doses ranging from 4/1 mg buprenorphine/naloxone to 24/6 mg buprenorphine/naloxone may be required; patients may require treatment indefinitely and should continue for as long as the patient continues to benefit 	2/0.5 mg, 8/2 mg sublingual tablets

Dosages (continued)

Drug	Dosing	Availability
lofexidine (Lucemyra)	<p>For the mitigation of opioid withdrawal symptoms:</p> <ul style="list-style-type: none"> – Three 0.18 mg tablets 4 times daily during peak withdrawal symptoms (typically 5 to 7 days after last opioid); adjust dose based on symptoms and side effects maintaining 5 to 6 hours between each dose; maximum total daily dose 2.88 mg (16 tablets); maximum single dose is 0.72 mg (4 tablets) – Treatment may continue for up to 14 days based on opioid withdrawal symptoms; gradual dose reduction over 2 to 4 days is recommended to discontinue lofexidine to avoid withdrawal symptoms 	0.18 mg tablets
naloxone hydrochloride injection (Evzio)	<p>Emergency treatment of opioid overdose, either known or suspected, as demonstrated by respiratory and/or central nervous system depression:</p> <ul style="list-style-type: none"> – Not intended as a substitute for emergency medical care but for immediate administration as emergency therapy when opioids may have been used – Dosage: 0.4 mg or 2 mg by intramuscular or subcutaneous injection only into the anterolateral aspect of the thigh of adult or pediatric patients, through clothing, if needed; for pediatric patients less than 1 year of age, the thigh muscle should be pinched while the dose is administered – If the voice instruction system does not operate properly, the intended dose of naloxone hydrochloride will still be delivered if the auto-injector is used according to printed instructions on the label <p>Immediately after administration, emergency medical care should be sought; additional doses may be administered every 2 to 3 minutes until arrival of emergency medical assistance</p>	<p>2 mg/0.4 mL solution in a pre-filled auto-injector (supplied as 2 Evzio 2 mg auto-injectors and a single Trainer)</p> <p>0.4 mg/mL, 2 mg/2 mL syringes (institutional use)*</p> <p>0.4 mg/mL single-dose vials*</p> <p>0.4 mg/mL multidose vials*</p>
naloxone hydrochloride nasal spray (Narcan)	<p>Emergency treatment of opioid overdose, either known or suspected, as demonstrated by respiratory and/or central nervous system depression: (Not intended as a substitute for emergency medical care but for immediate administration as emergency therapy when opioids may have been used)</p> <p>Administer 1 spray into a single nostril; may administer additional doses using a new nasal spray with each dose if there is no response or relapse occurs; additional doses may be administered every 2 to 3 minutes as needed until emergency assistance arrives</p>	4 mg/0.1 mL nasal spray (supplied as 2 blister packages per carton, with each blister containing a single nasal spray)

* Product intended for use by a healthcare provider in a healthcare setting or emergency situation; may be used to reverse opioid depression in a patient with a known or suspected overdose.

Dosages (continued)

Drug	Dosing	Availability
naltrexone hydrochloride tablets	<p>Opioid dependence:</p> <ul style="list-style-type: none"> – Initiate after completion of opioid detoxification and a minimum 7 to 10 day opioid-free interval for patients previously using short-acting opioids; since absence of an opioid drug in the urine is not a sufficient indication that a patient is opioid-free, a naloxone challenge test may be administered; if the challenge test is positive, do not initiate therapy; repeat the test in 24 hours – Initial dose 25 mg daily; if no evidence of withdrawal, initiate 50 mg (doses as low as 12.5 mg have been used initially-titrating by 12.5 mg daily until 50mg dose has been achieved) – Supervised alternate dosing schedules may be required; 50 mg daily on weekdays with 100 mg on Saturday; 100 mg every other day; 150 mg every third day <p>Alcohol dependence:</p> <p>50 mg once daily (following verification that patient is opioid-free); safety and efficacy established only in short-term (up to 12 weeks of therapy)</p>	50 mg tablets (scored)
naltrexone extended-release injectable suspension (Vivitrol)	<p>For the treatment of alcohol dependence in patients who are able to abstain from alcohol in an outpatient setting and for the prevention of relapse to opioid dependence following opioid detoxification:</p> <ul style="list-style-type: none"> – 380 mg intramuscularly by a HCP into the gluteal muscle every 4 weeks or once monthly; patients must be opioid-free a minimum of 7 to 10 days and should not be drinking alcohol at the time of therapy initiation 	380 mg vial per 4 mL diluent

Buprenorphine and buprenorphine/naloxone (Bunavail/Suboxone/Zubsolv) are administered as a single daily dose. When taken via the sublingual or buccal routes, buprenorphine and buprenorphine/naloxone tablets have similar clinical effects. However, due to differences in bioavailability, dosing adjustments are necessary for patients who switch between these formulations (tablet to film or film to tablet). A single Zubsolv 5.7/1.4 mg sublingual tablet provides equivalent buprenorphine exposure as 1 buprenorphine/naloxone (Suboxone) 8/2 mg sublingual tablet. While a Bunavail 4.2/0.7 mg buccal film is also equivalent to the buprenorphine exposure in 1 buprenorphine/naloxone 8/2 mg sublingual tablet, to ensure accurate dosing, equivalent dosing transitions should be made using the tables in the package inserts.

Buprenorphine contains no naloxone and may be preferred for use during induction therapy. Buprenorphine/naloxone may be the preferred medication for maintenance treatment during unsupervised administration.

Maintenance buprenorphine should be limited to those patients who cannot tolerate buprenorphine/naloxone (Bunavail/Suboxone/Zubsolv) due to naloxone hypersensitivity.

There is no maximum duration of maintenance treatment for buprenorphine extended-release injection (Sublocade) or buprenorphine/naloxone sublingual tablet and sublingual and buccal film (Bunavail, Suboxone, Zubsolv). For some patients, treatment may continue indefinitely. Patients should be advised of the potential for relapse following discontinuation of medication-assisted treatment of opioid dependence.

Buprenorphine/naloxone sublingual tablet and sublingual and buccal film (Bunavail, Suboxone, Zubsolv) should be prescribed based on a consideration of visit frequency; provision of multiple refills are not recommended early in treatment or without appropriate follow-up visits.

Buprenorphine sublingual tablets and buprenorphine/naloxone sublingual tablets and film should be placed under the tongue until they are dissolved; swallowing the tablets or film reduces the bioavailability of the drug. Buprenorphine/naloxone buccal film should be placed against the inside of the cheek, moistened prior to application of the film. The initial application should be supervised to assess the proper technique is demonstrated following the specific steps outlined in the medication guide. Future applications can be self-administered without supervision. Consider reducing the starting and titration dose by half in patients with severe hepatic impairment.

Patients taking short-acting opioids or heroin should initiate buprenorphine therapy not less than 4 hours after the patient last used opioids or (preferably) when early signs of withdrawal begin. For patients taking long-acting opioids, buprenorphine should be administered with signs of moderate opioid withdrawal and typically not less than 24 hours after the last exposure to a long-acting opioid. Buprenorphine/naloxone combination products may induce withdrawal for patients transitioning from methadone. Buprenorphine monotherapy is recommended in patients taking long-acting opioids and methadone.

For buprenorphine extended-release injection (Sublocade), delays of up to 2 weeks in subsequent dosing are not expected to have a significant clinical impact on treatment.

The dosage and frequency of lofexidine (Lucemyra) may be adjusted to decrease symptoms of opioid withdrawal to a maximum dose of 4 tablets 4 times daily (16 tablets/day, 2.88 mg). The maximum dosage should be reduced to 2 tablets 4 times daily in patients with moderate renal impairment (estimated creatinine clearance [CrCl], 30 to 89.9 mL/min/1.73 m²) and 1 tablet 4 times daily for severe renal impairment (CrCl < 30 mL/min/1.73 m²). The dose should be reduced for patients with hepatic impairment based on Child-Pugh scores. The maximum daily dose in mild impairment is 3 tablets 4 times daily, moderate impairment is 2 tablets 4 times daily, and severe impairment is 1 tablet 4 times daily.

The recommended dose of naltrexone injection is 380 mg delivered intramuscularly every 4 weeks or once a month. The injection must be administered by a healthcare professional as an intramuscular (IM) gluteal injection, alternating buttocks, using the carton components provided. The carton contains customized 1.5 or 2 inch needles; Vivitrol should not be injected using any other needle than the ones provided. If a patient misses a dose, the patient should be instructed to receive the next dose as soon as possible.

Pretreatment with oral naltrexone is not required before using naltrexone injection. No data are available for conversion from oral naltrexone or restarting treatment after discontinuation.

CLINICAL TRIALS

Articles were identified through searches performed on PubMed and review of information sent by the manufacturers. The search strategy included the FDA-approved use of all drugs in this class. Randomized, controlled, comparative trials of FDA-approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.

There are no published, blinded, comparative clinical studies meeting the above criteria available using buprenorphine/naloxone sublingual tablets (Zubsolv), buprenorphine/naloxone sublingual film (Suboxone), buprenorphine/naloxone buccal film (Bunavail), buprenorphine extended-release injection (Sublocade), lofexidine (Lucemyra), naltrexone HCl tablets, naloxone hydrochloride injection (Evzio), or naloxone nasal spray (Narcan).

buprenorphine (Subutex) and buprenorphine/naloxone tablets (Suboxone)

A multicenter, randomized, double-blind, placebo-controlled trial involving 326 patients with opiate addiction was conducted.¹³⁰ Patients were assigned to buprenorphine/naloxone 16/4 mg sublingual tablets, buprenorphine 16 mg, or placebo given daily for 4 weeks. The primary outcome measures were the percentage of urine samples negative for opiates and the subjects' self-reported craving for opiates. The trial was terminated early because buprenorphine/naloxone and buprenorphine alone were found to have greater efficacy than placebo. The proportion of urine samples that were negative for opiates was greater in the combination and buprenorphine-alone groups (17.8% and 20.7%, respectively) than in the placebo group (5.8%, $p < 0.001$ for both comparisons). The active-treatment groups also reported less opiate craving ($p < 0.001$ for both comparisons with placebo). Rates of adverse events were similar in the active-treatment and placebo groups.

buprenorphine sublingual (Suboxone/Subutex) and buprenorphine (Probuphine)

A randomized, double-blind, double-dummy, non-inferiority study (PRO-814) evaluated the efficacy of buprenorphine implant in adults meeting DSM-IV-TR criteria for opioid dependence (primary diagnosis) who were clinically stable on sublingual (SL) buprenorphine of 8 mg/day or less as Suboxone or Subutex.^{131,132,133} Clinical stability was defined as no reports or episodes of illicit opioid use, significant withdrawal symptoms, hospitalizations, emergency room visits, or crisis interventions; low or no desire to use illicit opioids; no positive urine toxicology for illicit opioids in past 90 days; transmucosal buprenorphine treatment for at least 6 months prior to randomization; compliance with clinic visits; stable living environment; participation in structured activity or job; and participation in peer support or cognitive behavioral program therapy. Patients were also assessed and measured to have minimal symptoms based on a withdrawal symptom score. Participants were randomized 1:1 to buprenorphine implant or continued SL buprenorphine ($n=177$), and visits occurred monthly for 6 months.

Supplemental dosing with open-label buprenorphine/naloxone SL tablets was permitted when clinically indicated. Urine toxicology screens (6 scheduled, 4 random) and patient self-reporting or opioid use were used to evaluate efficacy. The primary endpoint was the proportion of responders (defined as number of patients without opioid use in 4 out of 6 months). Response occurred in 87.6% of patients on SL buprenorphine compared to 96.4% on buprenorphine implant, meeting the 20% non-inferiority margin. Likewise, 63% of patients on buprenorphine implant compared to 64% of patients on SL buprenorphine had no evidence of illicit opioid use (treatment difference, 1%; 95% confidence interval [CI], -15 to 13). Fifteen patients in the implant group required supplemental SL buprenorphine compared to 13 individuals in the SL buprenorphine group. Notably, nearly 95% of patients were Caucasian, the majority were male, and approximately 75% stated their primary drug of abuse was a prescription opioid pain reliever. At entry, the dose of Suboxone/Subutex ranged from 2 to 8 mg/day of buprenorphine, with the majority of patients on an 8 mg/day dose.

naltrexone extended-release injectable suspension (Vivitrol) and buprenorphine/naloxone sublingual film (Suboxone)

A 24-week, randomized, open-label, controlled trial compared opioid relapse-free survival in 570 adult patients treated with naltrexone extended-release injectable suspension 380 mg every 28 days or buprenorphine/naloxone sublingual film at dosage of 8 mg to 24 mg of buprenorphine daily.¹³⁴ Participants had used non-prescribed opioids in the previous 30 days. Exclusion criteria included, but were not limited to, serious medical, psychiatric, or substance use disorders, concurrent methadone maintenance treatment (≥ 30 mg/day), chronic pain requiring opioids. Participants were stratified by treatment site and opioid use severity, then randomized 1:1 for treatment with naltrexone extended-release or buprenorphine/naloxone for continuation to the outpatient setting. Initial opioid detoxification protocols and lengths of stay varied by treatment site. Prior to the first injection of naltrexone, patients needed to be opioid-free for ≥ 3 days, have opioid-negative urine, and a negative naloxone challenge test. Buprenorphine/naloxone was initiated in an observed setting-based presence of withdrawal symptoms. Subsequent doses were dispensed in up to 2 week supplies through the study period. The primary outcome was the time to a relapse event after day 20 of randomization (relapse was defined as 4 consecutive weeks of non-study opioid use per urine toxicology or self-report or 7 consecutive days of self-reported use). Opioid-relapse events occurred in 65% naltrexone-treated patients compared to 75% of buprenorphine/naloxone-treated patients. For patients that successfully completed induction, the opioid-relapse event rate was 52% for the naltrexone group compared to 56% for the buprenorphine/naloxone group with no difference in relative hazard of relapse (HR 0.92, 95% CI 0.17-1.18). Opioid-relapse failures on day 21 occurred in 25% participants treated with naltrexone compared to 3% treated with buprenorphine/naloxone, suggesting the difference between the intention-to-treat population and per-protocol population differences occurred during the induction period.

META-ANALYSES

In 2016, a meta-analysis was completed to review randomized controlled trial data for the effectiveness of alpha₂-adrenergic agonists, including clonidine, lofexidine, guanfacine, and tizanidine, in the management of the acute phase of opioid withdrawal.¹³⁵ Twenty-six randomized, controlled trials representing 1,728 participants were included in the review. In 3 studies, the authors found evidence that alpha₂ adrenergic agonists were more effective than placebo at mitigating the symptoms of severe opioid withdrawal (risk ratio [RR], 0.32; 95% CI, 0.18 to 0.57). In these 3 studies, patients treated with alpha₂ adrenergic agonists were more likely to complete treatment than those treated with placebo (RR, 1.95; 95% CI, 1.34 to 2.84). There was insufficient data to provide a comparison of the alpha₂ adrenergic agonists for effectiveness, although experience with lofexidine in 3 trials supports decreased hypotensive adverse events for patients treated with lofexidine compared to clonidine.

SUMMARY

Buprenorphine products are partial opioid agonists effective for the treatment of opioid dependence disorders. Products are available in various sublingual formulations, a subdermal implant, and an extended-release injection. Availability is only through select prescribers who obtain a waiver from the US Substance Abuse and Mental Health Services Administration (SAMHSA) and hold a modified Drug Enforcement Administration (DEA) registration. Methadone, a full opioid receptor agonist, is also a widely used treatment for opioid dependence, but availability is restricted to methadone treatment programs.

Of the buprenorphine-containing products, buprenorphine sublingual tablet monotherapy is approved for treatment but is preferred in induction therapy only. Buprenorphine/naloxone buccal film (Bunavail), sublingual film (Suboxone), and sublingual tablets (Zubsolv) are all approved for both induction treatment and maintenance therapy. Generic equivalents of Suboxone (buprenorphine/naloxone) sublingual tablets (branded product no longer available) and buprenorphine extended-release injection (Sublocade) are approved for maintenance treatment only. Buprenorphine subdermal implant (Probuphine) offers an additional maintenance treatment option for patients stabilized on low-to-moderate doses of a transmucosal buprenorphine-containing product for a minimum of 3 months. Comparative data between formulations for induction or maintenance treatment are limited.

Lofexidine (Lucemyra) is the first non-opioid medication approved for the management of acute opioid withdrawal symptoms for adults after abrupt discontinuation of opioids. It is intended to mitigate the peak withdrawal symptoms 5 to 7 days after the last opioid dose and up to 14 days total.

Clinically, naltrexone is used to help maintain an opioid-free state in patients who are known opioid abusers in both oral (generic) and extended-release injectable (Vivitrol) forms. Both formulations are also approved for the treatment of alcohol dependence. Unlike an opioid agonist, naltrexone does not reinforce medication compliance and will not prevent withdrawal.

Medication-assisted treatment (MAT) for opioid addiction using a buprenorphine-containing product or naltrexone formulation should be accompanied by counseling and psychosocial support as part of a complete treatment program. There is no maximum treatment duration for the treatment of opioid

use disorder with the exception of 2 injections of buprenorphine subdermal implant (Probuphine). Maintenance treatment should occur as long as there is a benefit to the patient.

Although limited, data suggest that methadone and buprenorphine are both effective for the treatment of opioid dependence disorders. Patients with severe opioid dependence may be considered for methadone therapy. Choice of medication-assisted treatment of opioid dependence (e.g., buprenorphine, methadone, naltrexone) should be a shared decision between the clinician and patient and should consider patient preferences, patient safety, treatment history, and treatment setting.

Naloxone hydrochloride injection (Evzio) and naloxone hydrochloride nasal spray (Narcan) offer methods for emergency treatment for opioid overdose until medical treatment is obtained; however neither is a substitute for emergency medical care.

REFERENCES

- 1 Buprenorphine tablets [package insert]. Elizabeth, NJ; Actavis; February 2018.
- 2 Subutex [package insert]. North Chesterfield, VA; Indivior; October 2019.
- 3 Sublocade [package insert]. North Chesterfield, VA; Indivior; October 2019.
- 4 Probuphine [package insert]. South San Francisco, CA; Titan Pharmaceuticals; October 2019.
- 5 Bunavail [package insert]. Raleigh, NC; BioDelivery Sciences International; October 2019.
- 6 Suboxone film [package insert]. North Chesterfield, VA; Indivior; October 2019.
- 7 Zubsolv tablets [package insert]. Morristown, NJ; Orexo; October 2019.
- 8 Buprenorphine/naloxone tablets [package insert]. Elizabeth, NJ; Actavis; October 2019.
- 9 Lucemyra [package insert]. Louisville, KY; US WorldMeds; May 2018.
- 10 Evzio 2 mg [package insert]. Richmond, VA; Kaleo; October 2016.
- 11 Narcan nasal spray [package insert]. Radnor, PA; Adapt; September 2019.
- 12 Naltrexone tablet [package insert]. Durham, NC; Accord; February 2014.
- 13 Vivitrol [package insert]. Waltham, MA; Alkermes; September 2019.
- 14 HHS Acting Secretary Declares Public Health Emergency to Address National Opioid Crisis. Available at: <https://www.hhs.gov/about/news/2017/10/26/hhs-acting-secretary-declares-public-health-emergency-address-national-opioid-crisis.html>. Accessed December 26, 2019.
- 15 Key Substance Use and Mental Health Indicators in the United States: Results from the 2018 National Survey on Drug Use and Health. Available at: <https://www.samhsa.gov/data/sites/default/files/cbhsq-reports/NSDUHNationalFindingsReport2018/NSDUHNationalFindingsReport2018.pdf>. Accessed December 20, 2019.
- 16 Reus VI, Fochtmann LJ, Bukstein O, et al. The American Psychiatric Association Practice Guideline for the Pharmacological Treatment of Patients With Alcohol Use Disorder. Available at: <http://psychiatryonline.org/guidelines.aspx>. Accessed December 26, 2019.
- 17 FDA approves first buprenorphine implant for treatment of opioid dependence. Drugs@FDA. Available at: <https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm503719.htm>. Accessed December 26, 2019.
- 18 Sublocade [package insert]. North Chesterfield, VA; Indivior; October 2019.
- 19 Gowing L, Ali R, White JM, et al. Buprenorphine for managing opioid withdrawal. Cochrane Database Syst Rev. 2017; 2:CD002025. DOI: 10.1002/14651858.CD002025.pub2.
- 20 Zubsolv tablets [package insert]. Morristown, NJ; Orexo; October 2019.
- 21 Medication-Assisted Treatment (MAT). Available at: <http://www.samhsa.gov/medication-assisted-treatment>. Accessed December 26, 2019.
- 22 Federal Register. Vol. 81. No 131. Part III. Medication Assisted Treatment for Opioid Use Disorders. Available at: https://www.deadiversion.usdoj.gov/pubs/docs/SAMHSA_Regulations_275.pdf. Accessed December 26, 2019.
- 23 H.R.6 Available at: <https://www.congress.gov/115/bills/hr6/BILLS-115hr6enr.pdf>. Accessed December 20, 2019.
- 24 Available at: www.clinicalpharmacology-ip.com. Accessed December 26, 2019.
- 25 Medication-Assisted Treatment (MAT). Available at: <https://www.samhsa.gov/medication-assisted-treatment>. Accessed December 26, 2019.
- 26 Kampman K, Jarvis M. American Society of Addiction Medicine (ASAM) national practice guideline for the use of medications in the treatment of addiction involving opioid use. J Addict Med. 2015; 9(5): 358-367, DOI: 10.1097/ADM.000000000000166. Available at: <http://www.asam.org/quality-practice/guidelines-and-consensus-documents/npg/complete-guideline>. Accessed December 26, 2019.
- 27 Schuckit MA. Treatment of opioid-use disorders. N Engl J Med. 2016; 375(4): 357-368. DOI: 10.1056/NEJMra1604339.
- 28 The American Society of Addiction Medicine (ASAM) appropriate use of drug testing in clinical addiction medicine. Available at: <https://www.asam.org/quality-practice/guidelines-and-consensus-documents/drug-testing>. Accessed December 26, 2019.
- 29 World Health Organization. Guidelines for the identification and management of substance use and substance use disorders in pregnancy. Available at: http://www.who.int/substance_abuse/publications/pregnancy_guidelines/en/. Accessed December 26, 2019.
- 30 Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain – United States, 2016. MMWR Recomm Rep. 2016; 65(1): 1-49. DOI: 10.15585/mmwr.rr6501e1. Available at: <https://www.cdc.gov/drugoverdose/prescribing/guideline.html>. Accessed December 26, 2019.
- 31 Dowell D, Haegerich T, Chou R. No shortcuts to safer opioid prescribing. N Engl J Med. 2019; 380:2285-7. DOI: 10.1056/NEJMp1904190.
- 32 Califf, FDA top officials call for sweeping review of agency opioids policies. Available at: <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm484765.htm>. Accessed December 26, 2019.

-
- 33 Statement by FDA Commissioner Scott Gottlieb, MD, on new steps to advance the development of evidence-based, indication-specific guidelines to help guide appropriate prescribing of opioid analgesics. Available at: <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm617908.htm>. Accessed: December 26, 2019.
- 34 World Health Organization. Community Management of Overdose. Available at: http://www.who.int/substance_abuse/publications/management_opioid_overdose/en/. Accessed December 26, 2019.
- 35 Surgeon General's Advisory on Naloxone and Opioid Overdose. Available at: <https://www.surgeongeneral.gov/priorities/opioid-overdose-prevention/naloxone-advisory.html>. Accessed December 26, 2019.
- 36 Naloxone: The Opioid Reversal Drug that Saves Lives. <https://www.hhs.gov/opioids/prevention/safe-opioid-prescribing/index.html>. Accessed December 26, 2019.
- 37 Buprenorphine tablets [package insert]. Elizabeth, NJ; Actavis; February 2018.
- 38 Subutex [package insert]. North Chesterfield, VA; Indivior; October 2019.
- 39 Probuphine [package insert]. South San Francisco, CA; Titan Pharmaceuticals; October 2019.
- 40 Bunavail [package insert]. Raleigh, NC; BioDelivery Sciences International; October 2019.
- 41 Suboxone film [package insert]. North Chesterfield, VA; Indivior; October 2019.
- 42 Zubsolv tablets [package insert]. Morristown, NJ; Orexo; October 2019.
- 43 Buprenorphine/naloxone tablets [package insert]. Elizabeth, NJ; Actavis; October 2019.
- 44 Naltrexone tablet [package insert]. Durham, NC; Accord; February 2014.
- 45 Vivitrol [package insert]. Waltham, MA; Alkermes; September 2019.
- 46 Evzio 2 mg [package insert]. Richmond, VA; Kaleo; October 2016.
- 47 Narcan nasal spray [package insert]. Radnor, PA; Adapt; September 2019.
- 48 Sublocade [package insert]. North Chesterfield, VA; Indivior; October 2019.
- 49 Lucemyra [package insert]. Louisville, KY; US WorldMeds; May 2018.
- 50 Buprenorphine tablets [package insert]. Elizabeth, NJ; Actavis; February 2018.
- 51 Subutex [package insert]. North Chesterfield, VA; Indivior; October 2019.
- 52 Probuphine [package insert]. South San Francisco, CA; Titan Pharmaceuticals; October 2019.
- 53 Bunavail [package insert]. Raleigh, NC; BioDelivery Sciences International; October 2019.
- 54 Lucemyra [package insert]. Louisville, KY; US WorldMeds; May 2018.
- 55 Suboxone film [package insert]. North Chesterfield, VA; Indivior; October 2019.
- 56 Zubsolv tablets [package insert]. Morristown, NJ; Orexo; October 2019.
- 57 Buprenorphine/naloxone tablets [package insert]. Elizabeth, NJ; Actavis; October 2019.
- 58 Naltrexone tablet [package insert]. Durham, NC; Accord; February 2014.
- 59 Vivitrol [package insert]. Waltham, MA; Alkermes; September 2019.
- 60 Evzio 2 mg [package insert]. Richmond, VA; Kaleo; October 2016.
- 61 Narcan nasal spray [package insert]. Radnor, PA; Adapt; September 2019.
- 62 Sublocade [package insert]. North Chesterfield, VA; Indivior; October 2019.
- 63 Buprenorphine tablets [package insert]. Elizabeth, NJ; Actavis; February 2018.
- 64 Subutex [package insert]. North Chesterfield, VA; Indivior; October 2019.
- 65 Probuphine [package insert]. South San Francisco, CA; Titan Pharmaceuticals; October 2019.
- 66 Bunavail [package insert]. Raleigh, NC; BioDelivery Sciences International; October 2019.
- 67 Suboxone film [package insert]. North Chesterfield, VA; Indivior; October 2019.
- 68 Zubsolv tablets [package insert]. Morristown, NJ; Orexo; October 2019.
- 69 Buprenorphine/naloxone tablets [package insert]. Elizabeth, NJ; Actavis; October 2019.
- 70 Naltrexone tablet [package insert]. Durham, NC; Accord; February 2014.
- 71 Vivitrol [package insert]. Waltham, MA; Alkermes; September 2019.
- 72 Evzio 2 mg [package insert]. Richmond, VA; Kaleo; October 2016.
- 73 Narcan nasal spray [package insert]. Radnor, PA; Adapt; September 2019.
- 74 Sublocade [package insert]. North Chesterfield, VA; Indivior; October 2019.
- 75 Lucemyra [package insert]. Louisville, KY; US WorldMeds; May 2018.
- 76 Available at: <https://www.fda.gov/Drugs/DrugSafety/ucm575307.htm>. Accessed December 26, 2019.
- 77 Available at: <http://www.accessdata.fda.gov/scripts/cder/remis/index.cfm>. Accessed December 26, 2019.
- 78 Buprenorphine tablets [package insert]. Elizabeth, NJ; Actavis; February 2018.
- 79 Subutex [package insert]. North Chesterfield, VA; Indivior; October 2019.
- 80 Probuphine [package insert]. South San Francisco, CA; Titan Pharmaceuticals; October 2019.
- 81 Bunavail [package insert]. Raleigh, NC; BioDelivery Sciences International; October 2019.
- 82 Suboxone film [package insert]. North Chesterfield, VA; Indivior; October 2019.
- 83 Zubsolv tablets [package insert]. Morristown, NJ; Orexo; October 2019.
- 84 Buprenorphine/naloxone tablets [package insert]. Elizabeth, NJ; Actavis; October 2019.
- 85 Naltrexone tablet [package insert]. Durham, NC; Accord; February 2014.
- 86 Vivitrol [package insert]. Waltham, MA; Alkermes; September 2019.
- 87 Evzio 2 mg [package insert]. Richmond, VA; Kaleo; October 2016.
- 88 Narcan nasal spray [package insert]. Radnor, PA; Adapt; September 2019.
- 89 Sublocade [package insert]. North Chesterfield, VA; Indivior; October 2019.
- 90 Lucemyra [package insert]. Louisville, KY; US WorldMeds; May 2018.
- 91 Buprenorphine tablets [package insert]. Elizabeth, NJ; Actavis; February 2018.
- 92 Subutex [package insert]. North Chesterfield, VA; Indivior; October 2019.
- 93 Probuphine [package insert]. South San Francisco, CA; Titan Pharmaceuticals; October 2019.
- 94 Bunavail [package insert]. Raleigh, NC; BioDelivery Sciences International; October 2019.
-

-
- 95 Suboxone film [package insert]. North Chesterfield, VA; Indivior; October 2019.
- 96 Zubsolv tablets [package insert]. Morristown, NJ; Orexo; October 2019.
- 97 Buprenorphine/naloxone tablets [package insert]. Elizabeth, NJ; Actavis; October 2019.
- 98 Naltrexone tablet [package insert]. Durham, NC; Accord; February 2014.
- 99 Lucemyra [package insert]. Louisville, KY; US WorldMeds; May 2018.
- 100 Vivitrol [package insert]. Waltham, MA; Alkermes; September 2019.
- 101 Evzio 2 mg [package insert]. Richmond, VA; Kaleo; October 2016.
- 102 Narcan nasal spray [package insert]. Radnor, PA; Adapt; September 2019.
- 103 Sublocade [package insert]. North Chesterfield, VA; Indivior; October 2019.
- 104 Buprenorphine tablets [package insert]. Elizabeth, NJ; Actavis; February 2018.
- 105 Subutex [package insert]. North Chesterfield, VA; Indivior; October 2019.
- 106 Probuphine [package insert]. South San Francisco, CA; Titan Pharmaceuticals; October 2019.
- 107 Bunavail [package insert]. Raleigh, NC; BioDelivery Sciences International; October 2019.
- 108 Suboxone film [package insert]. North Chesterfield, VA; Indivior; October 2019.
- 109 Zubsolv tablets [package insert]. Morristown, NJ; Orexo; October 2019.
- 110 Buprenorphine/naloxone tablets [package insert]. Elizabeth, NJ; Actavis; October 2019.
- 111 Naltrexone tablet [package insert]. Durham, NC; Accord; February 2014.
- 112 Vivitrol [package insert]. Waltham, MA; Alkermes; September 2019.
- 113 Evzio 2 mg [package insert]. Richmond, VA; Kaleo; October 2016.
- 114 Narcan nasal spray [package insert]. Radnor, PA; Adapt; September 2019.
- 115 Sublocade [package insert]. North Chesterfield, VA; Indivior; October 2019.
- 116 Lucemyra [package insert]. Louisville, KY; US WorldMeds; May 2018.
- 117 Buprenorphine tablets [package insert]. Elizabeth, NJ; Actavis; February 2018.
- 118 Subutex [package insert]. North Chesterfield, VA; Indivior; October 2019.
- 119 Probuphine [package insert]. South San Francisco, CA; Titan Pharmaceuticals; October 2019.
- 120 Bunavail [package insert]. Raleigh, NC; BioDelivery Sciences International; October 2019.
- 121 Suboxone film [package insert]. North Chesterfield, VA; Indivior; October 2019.
- 122 Zubsolv tablets [package insert]. Morristown, NJ; Orexo; October 2019.
- 123 Buprenorphine/naloxone tablets [package insert]. Elizabeth, NJ; Actavis; October 2019.
- 124 Naltrexone tablet [package insert]. Durham, NC; Accord; February 2014.
- 125 Lucemyra [package insert]. Louisville, KY; US WorldMeds; May 2018.
- 126 Vivitrol [package insert]. Waltham, MA; Alkermes; September 2019.
- 127 Evzio 2 mg [package insert]. Richmond, VA; Kaleo; October 2016.
- 128 Narcan nasal spray [package insert]. Radnor, PA; Adapt; September 2019.
- 129 Sublocade [package insert]. North Chesterfield, VA; Indivior; October 2019.
- 130 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):949-58.
- 131 Probuphine [package insert]. South San Francisco, CA; Titan Pharmaceuticals; October 2019.
- 132 Psychopharmacology Drugs Advisory Committee to the FDA meeting materials. January 12, 2016. Available at: <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PsychopharmacologicDrugsAdvisoryCommittee/UCM500363.pdf>. Accessed December 26, 2019.
- 133 Rosenthal RN, Lofwall MR, Kim S, et al. Effect of buprenorphine implants on illicit opioid use among abstinent adults with opioid dependence treated with sublingual buprenorphine: a randomized clinical trial. *JAMA.* 2016; 316(3): 282-290. DOI: 10.1001/jama.2016.9382.
- 134 Lee JD, Nunes EV, Novo P, et al. Comparative effectiveness of extended-release naltrexone versus buprenorphine-naloxone for opioid relapse prevention (X:BOT): a multicenter, open-label, randomized controlled trial. *Lancet online.* November 14, 2017. DOI: 10.1016/S0140-6736(17)32812-X.
- 135 Gowing L, Farrell M, Ali R, et al. Alpha2-adrenergic agonists for the management of opioid withdrawal. *Cochrane Database of Systematic Reviews* 2016, Issue 5. DOI: 10.1002/14651858.CD002024.pub5.