



Opiate Dependence Treatments Therapeutic Class Review (TCR)

June 9, 2016

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MANAGEMENTSM

FDA-APPROVED INDICATIONS

Drug	Manufacturer	Indication
buprenorphine sublingual tablets ¹	generic	Treatment of opiate dependence and is preferred for induction only
buprenorphine implant (subdermal) (Probuphine®) ²	Braeburn	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)
buprenorphine/naloxone buccal film (Bunavail®) ³	BioDelivery Sciences International	Maintenance treatment of opiate dependence
buprenorphine/naloxone sublingual film (Suboxone®) ⁴	Indivior	Treatment of opiate dependence (induction and maintenance)
buprenorphine/naloxone sublingual tablets (Zubsolv®) ⁵	Orexo	Treatment of opiate dependence (induction and maintenance)
buprenorphine/naloxone sublingual tablets ⁶	generic	Maintenance treatment of opiate dependence
naltrexone hydrochloride tablets (ReVia®) ⁷	Duramed, generic	Treatment of opiate dependence Treatment of alcohol dependence in conjunction with a behavior modification program
naltrexone extended-release injectable suspension (Vivitrol®) ⁸	Alkermes	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
naloxone hydrochloride injection (Evzio®) ⁹	Kaleo, generic	Emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression
naloxone hydrochloride nasal spray (Narcan®) ¹⁰	Adapt	Emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression

Reckitt Benckiser has discontinued brand Subutex® buprenorphine sublingual (SL) tablets as they believe the mono product (product containing buprenorphine alone without naloxone) creates a greater risk of misuse, abuse, and diversion.

On September 18, 2012, Reckitt Benckiser voluntarily discontinued brand Suboxone (buprenorphine and naloxone) SL tablets due to increasing concerns of pediatric exposure, based on an analysis on accidental pediatric exposures data from the U.S. Poison Control Centers.¹¹ The rates of Suboxone SL tablet were 7.8 to 8.5 times higher depending on the study period. In July 2013, the FDA approved Zubsolv, buprenorphine and naloxone, SL tablets.

OVERVIEW

Although it may be the most publicized, heroin is not the only opiate that is abused. Prescription opiates, such as oxycodone, morphine, and hydrocodone, have become increasingly abused. The 2014 National Survey on Drug Use and Health (NSDUH) reported there was an estimated 27 million Americans 12 years and older who were current (past month) illicit drug users. Approximately 21.5 million people aged 12 or older in 2014 had Substance Use Disorder (SUD) in the past year, including 17 million people with an alcohol use disorder and 7.1 million people with an illicit drug use disorder. An estimated 2.6 million people aged 12 or older had both an alcohol use disorder and an illicit drug use disorder in the past year.¹²

Methadone is a full opiate receptor agonist that has been thoroughly studied and is widely used as treatment for opiate dependence. It is orally active, can be dosed once daily, and can suppress symptoms of opiate withdrawal while blocking the effects of other opiates. 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 opiates like respiratory depression.

Buprenorphine is a Schedule III narcotic under the Controlled Substances Act and has the same potential for abuse as other opioids. Both buprenorphine and buprenorphine/naloxone can be used for office-based detoxification from opiates and maintenance treatment for opiate dependency by specially trained and registered physicians. Like methadone, buprenorphine can suppress opiate withdrawal symptoms and block the effects of other opiates. 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.¹³ A formal evaluation of methadone is not within the scope of this review.

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 U.S. Substance Abuse and Mental Health Services Administration (SAMHSA), and notify the Secretary of Health and Human Services (HHS) 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.^{14,15}

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 1995.¹⁶ 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.

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.¹⁷

Recently, an implantable buprenorphine product (Probuphine) has been 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.¹⁸

PHARMACOLOGY^{19,20,21,22,23,24,25,26,27,28}

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 opiates.

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.

PHARMACOKINETICS^{29,30,31,32,33,34,35,36,37}

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
naloxone	low 46.7%*	45 (albumin)	5–6.25; 1.36 (± 0.32) [†]	glucuronidation, N-dealkylation, reduction	primarily urine
naltrexone	variable 5–40	21–28	biphasic naltrexone: 4 6β-naltrexol: 13	6β-naltrexol	primarily renal
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

† One pharmacokinetic study of a single subcutaneous or intramuscular injection (standard syringe) of naloxone (Evzio) in healthy adults

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 (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^{38,39,40,41,42,43,44,45,46}

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

Buprenorphine implant 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.

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. 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 opiates, buprenorphine may produce orthostatic hypotension in ambulatory patients.

Buprenorphine, like other potent opiates, 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 opiate 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.

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.

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. 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. Adrenal insufficiency cases have been reported in association with greater than 1 month of opioid use. If diagnosis of adrenal insufficiency is confirmed, the opioid should be titrated off to allow the adrenal function to recover.

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 kyphoscoliosis.

Deaths have occurred in opioid-naïve patients who received a 2 mg dose of buprenorphine sublingually for analgesia. Buprenorphine should not be used for analgesia. 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 abstinence syndrome 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.

Risk Evaluation and Mitigation Strategies (REMS)⁴⁷

There is a buprenorphine-containing transmucosal products for opioid dependence (BTOD) REMS. A medication guide will be dispensed with each buprenorphine, buprenorphine/naloxone, naltrexone extended-release injectable suspension and naloxone hydrochloride injectable prescription. Naltrexone ER injectable suspension is also subject to a communication plan. Other elements in place to ensure safe buprenorphine and buprenorphine/naloxone use include verification of safe use conditions and patient monitoring.

DRUG INTERACTIONS^{48,49,50,51,52,53,54,55}

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 sublingually be monitored for signs and symptoms of opiate withdrawal if inducers of CYP3A4 (e.g., efavirenz, phenobarbital, carbamazepine, phenytoin, rifampicin) are co-administered.

Patients receiving buprenorphine in the presence of other CNS depressants (including alcohol) may exhibit increased CNS depression.

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.

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^{56,57,58,59,60,61,62,63,64}

Drug	Headache	Abdominal Pain	Withdrawal Syndrome	Constipation	Nausea	Insomnia
buprenorphine	28-34 (22.4)	11.7 (6.5)	18.4-24 (37.4)	5-14 (2.8)	7-13.6 (11.2)	21.4-28 (15.9)
buprenorphine subdermal implant (Probuphine) [*]	> 5	nr	nr	> 5	> 5	nr
buprenorphine/naloxone SL film/tablet (Suboxone, generic)	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
naltrexone extended-release injectable suspension (Vivitrol)	3 (2)	nr [§]	nr	nr	reported	6 (1)
naltrexone hydrochloride (ReVia)	> 10	> 10	reported	< 10	> 10	> 10
naloxone hydrochloride injection (Evzio)	nr	reported	reported	reported	reported	nr
naloxone hydrochloride nasal spray (Narcan)	reported	reported	reported	reported	reported	nr

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 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.

[§] Abdominal pain not reported for opioid dependence data but reported for alcohol dependence.

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

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.

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.

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.

Additional adverse effects reported with naloxone hydrochloride (Narcan) nasal spray include hypertension, musculoskeletal pain, nasal dryness, nasal edema, nasal congestion, and nasal inflammation.

SPECIAL POPULATIONS^{65,66,67,68,69,70,71,72,73}

Pediatrics

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

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

The safety and effectiveness of Evzio auto-injector and Narcan nasal spray, both naloxone hydrochloride formulations, 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 Category

All agents in this class are Pregnancy Category C, with the exceptions of naloxone hydrochloride auto-injection (Evzio), which is Pregnancy Category B and naloxone hydrochloride nasal spray (Narcan) and buprenorphine implant (Probuphine) which do not have a Pregnancy Category. There is limited data with the use of Narcan in pregnant women and Narcan may precipitate withdrawal in the fetus. Likewise, there are no well-controlled studies of Probuphine in pregnant women.

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 implant (Probuphine) did not include patients with renal impairment.

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 is not required in mild to moderate hepatic impairment. Naltrexone extended-release injectable has not been evaluated in 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).

Geriatrics

The safety and efficacy of buprenorphine, naloxone, or naltrexone have not been studied adequately to determine if an older population would respond differently than younger patients. 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^{74,75,76,77,78,79,80,81,82,83}

Drug	Dosing	Availability
buprenorphine SL tablets	<p>For the prevention of undue symptoms of opiate agonist withdrawal during induction of opiate agonist dependence treatment:</p> <p>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> <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</p>	2 mg, 8 mg sublingual tablets
buprenorphine subdermal implant (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> <p>Buprenorphine implant should be used as part of a complete treatment program, including counseling and psychosocial support and 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</p> <ul style="list-style-type: none"> – 4 implants inserted subdermally 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 <p>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</p>	Implant kit: 4-sterile implants containing 74.2 mg (equivalent to 80mg 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 maintenance treatment of opioid dependence in patients who have been initially inducted using buprenorphine sublingual tablets:</p> <p>If the patient is switching from Suboxone sublingual tablets, the equivalency chart in the package insert should be followed</p> <p>Adults: 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)</p> <p>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</p>	2.1/0.3 mg, 4.2/0.7 mg, 6.3/1 mg buccal films (citrus flavor)
buprenorphine / naloxone SL film (Suboxone)	<p>For the induction of opiate agonist dependence treatment:</p> <p>For patients dependent on short-acting opioid products or heroin in opioid withdrawal:</p> <ul style="list-style-type: none"> – Day 1: up to 8/2 mg in divided doses; – Day 2: up to 16/4 mg as a single dose <p>To avoid precipitating withdrawal syndrome, the first dose should be started when objective signs of moderate withdrawal appear</p> <p>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</p> <p>For the maintenance treatment:</p> <p>Adults and Adolescents ≥ 16 years: Following induction to opioid dependence treatment, a target dose of 16/4 mg buprenorphine/ naloxone sublingually once daily is suggested; however, doses ranging from 4–24 mg/day of the buprenorphine component may be required</p> <p>Titrate dosage in increments of 2–4 mg/day of buprenorphine to a dose that holds the patient in treatment and suppresses opiate 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</p>	2/0.5 mg, 4/1 mg, 8/2 mg, 12/3 mg sublingual films

Dosages (continued)

Drug	Dosing	Availability
<p>buprenorphine / naloxone SL tablets (Zubsolv)</p>	<p>For the induction of opiate agonist treatment: Buprenorphine monotherapy is recommended for patients dependent on long-acting opioid products and/or methadone; buprenorphine/naloxone combination products contain naloxone, which is absorbed in small amounts by the sublingual route and could cause worse precipitated and prolonged withdrawal; after induction, patients can then be transitioned to once daily sublingual tablet</p> <p>Patients dependent on heroin or other short-acting opioid products may be induced on buprenorphine/naloxone SL tablets or with sublingual buprenorphine monotherapy; the dose should be initiated when moderate signs of opiate withdrawal appear; not less than 6 hours after the patient last used opioids</p> <p>To avoid precipitating withdrawal, induction should be initiated when objective and clear signs of withdrawal are evident</p> <ul style="list-style-type: none"> – Day 1: up to 5.7/1.4 mg in divided doses starting with 1.4/0.36 mg (additional dosing details are available in the prescribing information); – Day 2: single dose up to 11.4/2.9 mg is recommended <p>For the maintenance of opiate agonist dependence treatment: Adults and Adolescents ≥ 16 years: Following induction to opioid dependence treatment, a target dose of 11.4/2.9 mg buprenorphine/naloxone is recommended; however, doses ranging from 2.8/0.72 mg buprenorphine/naloxone to 17.1/4.2 mg buprenorphine/naloxone may be required</p> <p>Titrate dose in increments of 1.4/0.36 mg or 2.8/0.72 mg of buprenorphine/naloxone to a dose that holds the patient in treatment and suppresses opiate withdrawal symptoms; doses above 17.1/4.2 mg per day of buprenorphine/naloxone have not shown to provide any additional clinical benefit</p>	<p>1.4/0.36 mg, 2.9/7.1 mg, 5.7/1.4 mg, 8.6/2.1 mg, 11.4/2.9 mg sublingual tablets</p>
<p>buprenorphine / naloxone SL tablets</p>	<p>For the maintenance of opiate agonist dependence treatment: Adults and Adolescents ≥ 16 years: Following induction to opioid dependence treatment, a target dose of 16/4 mg buprenorphine/naloxone sublingually once daily is suggested; however, doses ranging from 4–24 mg/day of the buprenorphine component and 1–6 mg/day of naloxone may be required</p> <p>Titrate dose in increments of 2–4 mg/day of buprenorphine to a dose that holds the patient in treatment and suppresses opiate withdrawal symptoms; higher dosages (12–16 mg/day of buprenorphine) have been associated with reduced opiate craving and fewer opiate-positive urine tests</p>	<p>2/0.5 mg, 8/2 mg sublingual tablets</p>

Dosages (continued)

Drug	Dosing	Availability
naltrexone hydrochloride tablets (ReVia)	<p>Opiate dependence:</p> <p>Induction of therapy for opiate cessation: Initiate induction regimen after completion of opiate detoxification and verification patient is opiate free 25 mg initially; 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)</p> <p>Maintenance of therapy for opiate cessation: 50 mg daily following induction</p> <p>Alcohol dependence:</p> <p>50 mg once daily (following verification that patient is opiate-free); safety and efficacy established only in short-term (up to 12 weeks of therapy)</p> <p>Before prescribing: patients must be opioid free for a minimum of 7 to 10 days prior to initiation of therapy; 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</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> <p>380 mg intramuscularly every 4 weeks or once monthly; inject into the gluteal muscle and alternate buttocks for each subsequent injection; patients must be opioid-free and should not be drinking alcohol at the time of therapy initiation</p>	380 mg vial per 4 mL diluent
naloxone hydrochloride injection (Evzio)	<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>Dosage: 0.4 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</p> <p>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> <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>	0.4 mg/0.4 mL solution in a pre-filled auto-injector (supplied as 2 Evzio 0.4 mg auto-injectors and a single Trainer)

Dosages (continued)

Drug	Dosing	Availability
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, each containing a single nasal spray, in a carton)

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 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.

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.

Patients taking short-acting opiates or heroin should initiate buprenorphine therapy at least 4 hours after the patient last used opiates or (preferably) when early signs of withdrawal begin. For patients taking methadone or other long-acting opiates, there is little clinical experience to draw from in order to provide guidance.

The recommended dose of naltrexone injection is 380 mg delivered intramuscularly every 4 weeks or once a month. The injection should be administered by a health care 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 naltrexone HCl tablets, buprenorphine/naloxone sublingual tablets (Zubsolv), buprenorphine/naloxone film (Suboxone), naltrexone extended-release injectable suspension (Vivitrol), buprenorphine/naloxone buccal film (Bunavail), 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.⁸⁴ 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.^{85,86,87} 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.

SUMMARY

Buprenorphine products are effective therapies for the treatment of opiate dependence disorders. Clinically, naltrexone is used to help maintain an opiate-free state in patients who are known opiate abusers. Naltrexone extended-release injectable suspension is of greatest benefit in patients who take the drug as part of a comprehensive occupational rehabilitative program or other compliance-enhancing program. Unlike methadone or levo-alpha-acetyl-methadol (LAAM), naltrexone does not reinforce medication compliance and will not prevent withdrawal. Patients with severe opiate dependence may be considered for methadone therapy. Buprenorphine subdermal implant (Probuphine) 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.

Naloxone hydrochloride injection (Evzio) and naloxone hydrochloride nasal spray (Narcan) offer methods for emergency treatment for opioid overdose until medical treatment is obtained.

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