Opiate Dependence Treatments
Therapeutic Class Review (TCR)

June 5, 2017

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### FDA-APPROVED INDICATIONS

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<th>Indication</th>
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<td>buprenorphine sublingual tablets¹</td>
<td>generic</td>
<td>Treatment of opiate dependence (preferred for induction only)</td>
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<tr>
<td>buprenorphine implant (subdermal) (Probuphine²)²*</td>
<td>Braeburn</td>
<td>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)</td>
</tr>
<tr>
<td>buprenorphine/naloxone buccal film (Bunavail³)³</td>
<td>BioDelivery Sciences International</td>
<td>Treatment of opiate dependence (induction and maintenance)</td>
</tr>
<tr>
<td>buprenorphine/naloxone sublingual film (Suboxone⁴)⁴</td>
<td>Indivior</td>
<td>Treatment of opiate dependence(.induction and maintenance)</td>
</tr>
<tr>
<td>buprenorphine/naloxone sublingual tablets (Zubsolv⁵)⁵</td>
<td>Orexo</td>
<td>Treatment of opiate dependence (induction and maintenance)</td>
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<tr>
<td>buprenorphine/naloxone sublingual tablets⁶</td>
<td>generic</td>
<td>Maintenance treatment of opiate dependence</td>
</tr>
<tr>
<td>naloxone hydrochloride injection† (Evzio⁷)⁷</td>
<td>Kaleo</td>
<td>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</td>
</tr>
<tr>
<td>naloxone hydrochloride nasal spray‡ (Narcan⁸)⁸</td>
<td>Adapt</td>
<td>Emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression</td>
</tr>
<tr>
<td>naltrexone hydrochloride tablets (ReVia⁹)¹⁰,¹¹</td>
<td>Duramed, generic</td>
<td>Treatment of opiate dependence Treatment of alcohol dependence in conjunction with a behavior modification program</td>
</tr>
<tr>
<td>naltrexone extended-release injectable suspension (Vivitrol¹²)¹²</td>
<td>Alkermes</td>
<td>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</td>
</tr>
</tbody>
</table>

* 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.

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.¹³ 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 2015 National Survey on Drug Use and Health (NSDUH) reported there was an estimated 27.1 million Americans 12 years and older who were current (past month) illicit drug users. Approximately 20.8 million people aged 12 or older in 2015 had substance use disorder (SUD) in the past year, including 15.7 million people with an alcohol use disorder and 7.7 million people with an illicit drug use disorder. Of those with a SUD in the past year, approximately 1 in 8 people aged 12 or older had both an alcohol use disorder and an illicit drug use disorder.¹⁴

Methadone, a Schedule II controlled substance under the Controlled Substances Act (CSA), 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. 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 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.¹⁵ 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.¹⁶ 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.¹⁷ 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.¹⁸,¹⁹ 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 Department of Health and Human Services (HHS) increased this patient limit to 275 patients.

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 1995.²⁰ 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 medication-assisted treatment, including training courses for buprenorphine use and opioid prescribing courses. 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. 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. Despite the availability of multiple guidelines and resources for the initiation and management of medications for opioid use disorder, there is no consensus on the ideal duration of maintenance therapy. 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.

The World Health Organization (WHO) has published guidelines on the identification and management of substance use disorders in pregnancy. 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. 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.

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. 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. 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.

Expanding 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).

**PHARMACOLOGY**

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\textsuperscript{41,42,43,44,45,46,47,48,49,50,51,52}

<table>
<thead>
<tr>
<th>Drug</th>
<th>Bioavailability (%)</th>
<th>Protein Binding (%)</th>
<th>Half-Life (hours)</th>
<th>Metabolism (Active Metabolite)</th>
<th>Elimination (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>buprenorphine</td>
<td>variable</td>
<td>96 (alpha, beta globulin)</td>
<td>24–48</td>
<td>N-dealkylation, glucuronidation (norbuprenorphine)</td>
<td>urine: 30; Feces: 69</td>
</tr>
<tr>
<td>naloxone</td>
<td>low 46.7%\textsuperscript{*}</td>
<td>45 (albumin)</td>
<td>5–6.25; 1.5–1.6\textsuperscript{†}</td>
<td>glucuronidation, N-dealkylation, reduction</td>
<td>primarily urine</td>
</tr>
<tr>
<td>naltrexone</td>
<td>variable 5–40</td>
<td>21–28</td>
<td>biphasic</td>
<td>6β-naltrexol</td>
<td>primarily renal</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>naltrexone: 4</td>
<td>6β-naltrexol</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>6β-naltrexol: 13</td>
<td>6β-naltrexol, is mediated by dihydrodiol dehydrogenase</td>
<td></td>
</tr>
<tr>
<td>naltrexone extended-release injectable suspension</td>
<td>low 21</td>
<td>5–10 days</td>
<td>6β-naltrexol, is mediated by dihydrodiol dehydrogenase</td>
<td>primarily urine</td>
<td></td>
</tr>
</tbody>
</table>

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

\textsuperscript{†} Includes both 0.4 mg and 2 mg doses 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 (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\textsuperscript{53,54,55,56,57,58,59,60,61,62,63,64}

Buprenorphine and buprenorphine/naloxone (Bunavail/Suboxone/Zubsolv/generic) 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 are 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. 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.

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 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.

Risk Evaluation and Mitigation Strategies (REMS)\(^6\)

There is a buprenorphine-containing transmucosal products for opioid dependence (BTOD) REMS that includes the following medications: buprenorphine tablets and buprenorphine/naloxone sublingual tablets (Zubsolv, generics) 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 of the 3 REMS programs 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. Naltrexone ER injectable suspension (Vivitrol) also has a REMS program consisting of a medication guide and a communication plan.
**DRUG INTERACTIONS**

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. **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.**

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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Headache</th>
<th>Abdominal Pain</th>
<th>Withdrawal Syndrome</th>
<th>Constipation</th>
<th>Nausea</th>
<th>Insomnia</th>
</tr>
</thead>
<tbody>
<tr>
<td>buprenorphine</td>
<td>28-34 (22.4)</td>
<td>11.7 (6.5)</td>
<td>18.4-24 (37.4)</td>
<td>5-14 (2.8)</td>
<td>7-13.6 (11.2)</td>
<td>21.4-28 (15.9)</td>
</tr>
<tr>
<td>buprenorphine subdermal implant (Probuphine)*</td>
<td>&gt; 5</td>
<td>nr</td>
<td>nr</td>
<td>&gt; 5</td>
<td>&gt; 5</td>
<td>nr</td>
</tr>
<tr>
<td>buprenorphine/naloxone SL film/tablet (Suboxone, generic)</td>
<td>36.4 (22.4)</td>
<td>11.2 (6.5)</td>
<td>25.2 (37.4)</td>
<td>12.1 (2.8)</td>
<td>15 (11.2)</td>
<td>14 (15.9)</td>
</tr>
<tr>
<td>buprenorphine/naloxone SL tablet (Zubsov)†</td>
<td>7 (7)</td>
<td>reported</td>
<td>reported</td>
<td>reported</td>
<td>5 (6)</td>
<td>reported</td>
</tr>
<tr>
<td>buprenorphine/naloxone buccal film (Bunavail)‡</td>
<td>≥ 5</td>
<td>nr</td>
<td>≥ 5</td>
<td>&gt; 1 to &lt; 5</td>
<td>nr</td>
<td>&gt; 1 to &lt; 5</td>
</tr>
<tr>
<td>naloxone hydrochloride injection (Evzio)§</td>
<td>nr</td>
<td>reported</td>
<td>reported</td>
<td>reported</td>
<td>reported</td>
<td>nr</td>
</tr>
<tr>
<td>naloxone hydrochloride nasal spray (Narcan)§</td>
<td>reported</td>
<td>reported</td>
<td>reported</td>
<td>reported</td>
<td>reported</td>
<td>nr</td>
</tr>
<tr>
<td>naltrexone extended-release injectable suspension (Vivitrol)</td>
<td>3 (2)</td>
<td>nr †</td>
<td>nr</td>
<td>nr</td>
<td>reported</td>
<td>6 (1)</td>
</tr>
<tr>
<td>naltrexone hydrochloride (ReVia)</td>
<td>&gt; 10</td>
<td>&gt; 10</td>
<td>reported</td>
<td>&lt; 10</td>
<td>&gt; 10</td>
<td>&gt; 10</td>
</tr>
</tbody>
</table>

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.
§ 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.

In clinical trials, few differences in the adverse event profile were noted among Suboxone sublingual film, Zubsov 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 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 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, rhinolalgia, xeroderma, and nasal inflammation.

**SPECIAL POPULATIONS**

**Pediatrics**

The safety and effectiveness of buprenorphine 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 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 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**

Buprenorphine sublingual tablets are Pregnancy Category C, and naloxone hydrochloride auto-injection 0.4 mg (Evzio) is Pregnancy Category B. Buprenorphine/naloxone buccal film (Bunavail), buprenorphine/naloxone sublingual film (Suboxone), buprenorphine/naloxone sublingual tablets (generic, Zubsolv), naloxone hydrochloride nasal spray (Narcan), naloxone hydrochloride auto-injection 2 mg (Evzio), and buprenorphine implant (Probuphine) do not have an assigned 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. Previously, buprenorphine/naloxone buccal film and tablets (Bunavail, Suboxone, Zubsolv) were assigned Pregnancy Category C, but the labeling was replaced with descriptive information in accordance with the Pregnancy and Lactation Labeling Rule (PLLRR). While there are no well-controlled studies of buprenorphine/naloxone, limited published data on use of buprenorphine have not shown an increased risk of major fetal malformations when used by pregnancy 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. Dosing 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 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.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosing</th>
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| buprenorphine SL tablets | **For the prevention of undue symptoms of opiate agonist withdrawal during induction of opiate agonist dependence treatment:**  
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  
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 | 2 mg, 8 mg sublingual tablets |
| buprenorphine implant, subdermal (Probuphine) | **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)  
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  
– 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  
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 80mg of buprenorphine HCl; 26 mm by 2.5 mm) and 1 disposable applicator |
**Dosages (continued)**

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<th>Drug</th>
<th>Dosing</th>
<th>Availability</th>
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| **buprenorphine / naloxone buccal film (Bunavail)** | **For the induction of opiate agonist dependence treatment:**  
- For patients dependent on short-acting opioid products or heroin in opioid withdrawal:  
  - Day 1: up to 4.2/0.7 mg in divided doses;  
  - 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 opioid)  
- For patients dependent on long-acting opioid products and/or methadone, 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 buccal film  
  Additional titration details are outlined in the prescribing information  
  Medication should be prescribed based on a consideration of visit frequency; provision of multiple refill is not recommended early in treatment or without appropriate follow-up visits  
- **For the maintenance treatment of opioid dependence in patients who have been initially inducted using buprenorphine sublingual tablets:**  
  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  
  Adults: 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  
  **There is no maximum duration of maintenance treatment; 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** | 2.1/0.3 mg, 4.2/0.7 mg, 6.3/1 mg buccal films (citrus flavor) |
### Dosages (continued)

<table>
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<tr>
<th>Drug</th>
<th>Dosing</th>
<th>Availability</th>
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<tr>
<td>buprenorphine / naloxone SL film (Suboxone)</td>
<td><strong>For the induction of opiate agonist dependence treatment:</strong>&lt;br&gt;For patients dependent on short-acting opioid products or heroin in opioid withdrawal:&lt;br&gt; - Day 1: up to 8/2 mg in divided doses;&lt;br&gt; - Day 2: up to 16/4 mg as a single dose&lt;br&gt;<strong>To avoid precipitating withdrawal syndrome, the first dose should be started when objective signs of moderate withdrawal appear</strong>&lt;br&gt;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&lt;br&gt;<strong>Additional titration details are outlined in the prescribing information</strong>&lt;br&gt;<strong>For the maintenance treatment:</strong>&lt;br&gt;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&lt;br&gt;<strong>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 dropout of patients during the induction period</strong></td>
<td>2/0.5 mg, 4/1 mg, 8/2 mg, 12/3 mg sublingual films</td>
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### Dosages (continued)

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<tr>
<th>Drug</th>
<th>Dosing</th>
<th>Availability</th>
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| buprenorphine / naloxone SL tablets (Zubsolv) | **For the induction of opiate agonist dependence 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  
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  
To avoid precipitating withdrawal, induction should be initiated when objective and clear signs of withdrawal are evident  
- 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  
**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 2.9/0.71 mg buprenorphine/naloxone to 17.1/4.2 mg buprenorphine/naloxone may be required  
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 opiate withdrawal symptoms; doses above 17.1/4.2 mg per day of buprenorphine/naloxone have not shown to provide any additional clinical 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 | **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  
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 | 2/0.5 mg, 8/2 mg sublingual tablets |
### Dosages (continued)

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<tr>
<th>Drug</th>
<th>Dosing</th>
<th>Availability</th>
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<tbody>
<tr>
<td>naltrexone hydrochloride tablets (ReVia)</td>
<td><strong>Opiate dependence:</strong></td>
<td>50 mg tablets (scored)</td>
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<tr>
<td></td>
<td>Induction of opiate agonist dependence treatment: Initiate induction</td>
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<td></td>
<td>regimen after completion of opiate detoxification and verification</td>
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<td>patient is opiate free 25 mg initially; if no evidence of withdrawal,</td>
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<td>initiate 50 mg (doses as low as 12.5 mg have been used initially-</td>
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<td>titrating by 12.5 mg daily until 50mg dose has been achieved)</td>
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<td></td>
<td>Maintenance of opiate agonist dependence treatment: 50 mg daily</td>
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<td></td>
<td>following induction</td>
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<td><strong>Alcohol dependence:</strong></td>
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<td>50 mg once daily (following verification that patient is opiate-free);</td>
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<td>safety and efficacy established only in short-term (up to 12 weeks of</td>
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<td>therapy)</td>
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<td>Before prescribing: patients must be opioid free for a minimum of 7 to</td>
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<td>10 days prior to initiation of therapy; since absence of an opioid drug</td>
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<td>in the urine is not a sufficient indication that a patient is opioid-free,</td>
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<td>a naloxone challenge test may be administered; if the challenge test is</td>
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<td>positive, do not initiate therapy; repeat the test in 24 hours</td>
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<tr>
<td>naltrexone extended-release injectable</td>
<td>**For the treatment of alcohol dependence in patients who are able to</td>
<td>380 mg vial per 4 mL diluent</td>
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<td>suspension (Vivitrol)</td>
<td>abstain from alcohol in an outpatient setting and for the prevention of</td>
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<td>relapse to opioid dependence following opioid detoxification:</td>
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<td>380 mg intramuscularly every 4 weeks or once monthly; inject into the</td>
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<td>gluteal muscle and alternate buttocks for each subsequent injection;</td>
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<td>patients must be opioid-free and should not be drinking alcohol at the</td>
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<td>time of therapy initiation</td>
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<td>naloxone hydrochloride injection (Evzio)</td>
<td><strong>Emergency treatment of opioid overdose, either known or suspected,</strong></td>
<td>0.4 mg/0.4 mL solution in a pre-</td>
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<td>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)</td>
<td>filled auto-injector (supplied as 2 Evzio 0.4 mg auto-injectors and a single Trainer), 2 mg/0.4 mL solution in a pre-filled auto-injector (supplied as 2 Evzio 2 mg auto-injectors and a single Trainer)</td>
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<td>Dosage: 0.4 mg or 2 mg by intramuscular or subcutaneous injection only</td>
<td>0.4 mg/mL, 2 mg/2 mL syringes (institutional use)*</td>
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<td>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</td>
<td>0.4 mg/mL single-dose vials*</td>
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<td></td>
<td>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 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</td>
<td>0.4 mg/mL multidose vials*</td>
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</table>

*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)

<table>
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<tr>
<th>Drug</th>
<th>Dosing</th>
<th>Availability</th>
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</thead>
<tbody>
<tr>
<td>naloxone hydrochloride nasal spray (Narcan)</td>
<td>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) 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</td>
<td>2 mg/0.1 mL nasal spray (supplied as 4 blister packages per carton, with each blister containing a single nasal spray) and 4 mg/0.1 mL nasal spray (supplied as 2 blister packages per carton, with each blister containing a single nasal spray)</td>
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</tbody>
</table>

Buprenorphine and buprenorphine/naloxone (Bunavail/Suboxone/Zubsolv/generic) 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/generic) 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 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 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.\(^\text{114}\) 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.\(^\text{115,116,117}\) 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 programs.
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 and are partial opioid agonists. These are available in various sublingual formulations but are only available through select prescribers who obtain a waiver from the U.S. Substance Abuse and Mental Health Services Administration (SAMHSA) and hold a modified Drug Enforcement Administration (DEA) registration. Methadone, a full opiate receptor agonist, is also a widely used treatment for opiate 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) 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.

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

Although limited, data suggest that methadone and buprenorphine are both effective for the treatment of opiate dependence disorders. Patients with severe opiate 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. Both are approved in 2 different strengths; however, naloxone nasal spray 2 mg (lower strength) carries a limitation of use stating it 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.

REFERENCES

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Opiate Dependence Treatments Review – June 2017

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