

# Opiate Dependence Treatments

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## Opiate Dependence Treatments

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### ***FDA-Approved Indications***

<b>Drug</b>	<b>Manufacturer</b>	<b>Indication</b>
buprenorphine (Subutex <sup>®</sup> ) <sup>2</sup>	generic	Treatment of opiate dependence
buprenorphine/ naloxone tablets (Suboxone <sup>®</sup> ) <sup>3</sup>	Reckitt Benckiser	Treatment of opiate dependence
buprenorphine/ naloxone film (Suboxone <sup>®</sup> ) <sup>4</sup>	Reckitt Benckiser	Treatment of opiate dependence

### ***Overview***

Although it may be the most publicized, heroin is not the only opiate that is abused. Prescription opiates such as oxycodone, morphine, and propoxyphene have become increasingly abused. The 2003 National Survey on Drug Use and Health found that there were approximately 31.2 million individuals who reported non-medical use of prescription pain relievers in their lifetime, which was higher than the rate of lifetime heroin use.<sup>5</sup>

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. Both buprenorphine (Subutex) and buprenorphine/naloxone (Suboxone) 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 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.<sup>6</sup> A formal evaluation of methadone is not within the scope of this review.

In order to become a qualified practitioner, physicians must be licensed under State law to practice medicine and obtain a waiver from the U.S. Substance Abuse and Mental Health Services Administration (SAMHSA) to prescribe or dispense buprenorphine. Such practitioners hold a modified Drug Enforcement Administration (DEA) registration in which they are designated by a unique identifier.

**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 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 (Suboxone) was formulated in order to prevent patients from abusing buprenorphine in combination with other opiates.

**Pharmacokinetics**<sup>7,8,9</sup>

Drug	Bioavailability	Protein Binding (%)	Half-Life (hours)	Metabolism (Active Metabolite)	Elimination (%)
buprenorphine	variable	96 (alpha, beta globulin)	32.8-37	N-dealkylation, glucuronidation (norbuprenorphine)	Urine: 30 Feces: 69
naloxone	low	45 (albumin)	1.1-6.2	glucuronidation, N-dealkylation, reduction	N/A

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

**Contraindication/Warnings**<sup>10,11,12</sup>

Buprenorphine (Subutex) and buprenorphine/naloxone (Suboxone) are contraindicated in patients who have been shown to be hypersensitive to buprenorphine. Buprenorphine/naloxone is also contraindicated in patients who have been shown to be hypersensitive to naloxone.

Patients receiving buprenorphine in the presence of other narcotic analgesics, general anesthetics, benzodiazepines, phenothiazines, other tranquilizers, sedative/hypnotics or other 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.

Significant respiratory depression has been associated with buprenorphine, particularly by the intravenous route. 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).

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.

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.

**Risk Evaluation and Mitigation Strategies (REMS):**

A medication guide will be dispensed with each buprenorphine/naloxone prescription. Other elements in place to ensure safe use include verification of safe use conditions and patient monitoring.

***Drug Interactions***<sup>13,14,15</sup>

Buprenorphine is metabolized to norbuprenorphine by cytochrome CYP 3A4. Because CYP 3A4 inhibitors may increase plasma concentrations of buprenorphine, patients already on CYP 3A4 inhibitors should be closely monitored and may require buprenorphine (Subutex) or buprenorphine/naloxone (Suboxone) 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.

***Adverse Effects***<sup>16,17</sup>

Drug	Headache	Abdominal Pain	Withdrawal Syndrome	Constipation	Nausea	Insomnia
buprenorphine (Subutex)	29.1 (22.4)	11.7 (6.5)	18.4 (37.4)	7.8 (2.8)	13.6 (11.2)	21.4 (15.9)
buprenorphine/naloxone (Suboxone tablets)	36.4 (22.4)	11.2 (6.5)	35.2 (37.4)	12.1 (2.8)	15.0 (11.2)	14.0 (15.9)

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.

***Special Population***<sup>18,19,20</sup>

**Pediatrics**

The safety and effectiveness of buprenorphine (Subutex) or buprenorphine/naloxone (Suboxone) in patients below the age of 16 have not been established.

**Pregnancy Category: C**

### Nursing Mothers

Use of high doses of sublingual buprenorphine in pregnant women showed that buprenorphine passes into the mother's milk. Breast-feeding is therefore not advised in mothers treated with buprenorphine or buprenorphine/naloxone.

### Hepatic Impairment

Dosage should be adjusted in this population, with patients monitored for symptoms of opiate withdrawal.

### **Dosages**<sup>21,22,23</sup>

Buprenorphine (Subutex) and buprenorphine/naloxone (Suboxone) are administered as a single daily dose. The recommended target dose is 16 mg of buprenorphine daily, but can be in the range of 4 mg to 24 mg daily. When taken sublingually, buprenorphine and buprenorphine/naloxone tablets have similar clinical effects and are interchangeable. However, the potential for greater bioavailability with buprenorphine/naloxone film exists. Dosing adjustments may be necessary for patients who switch between these two formulations. 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.

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.

Patients taking short-acting opiates or heroin should initiate buprenorphine therapy at least four 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.

Buprenorphine is available as 2 mg and 8 mg sublingual tablets. Buprenorphine/Naloxone is available as 2 mg/0.5 mg and 8 mg/2 mg sublingual tablets and sublingual films.

### **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 percent 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/funding must be considered, the studies in this review have also been evaluated for validity and importance.

There are no clinical studies available using the buprenorphine/naloxone film formulation.

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

A multicenter, randomized, double-blind, placebo-controlled trial involving 326 patients with opiate addiction was conducted.<sup>24</sup> Patients were assigned to buprenorphine/naloxone 16 mg/4 mg sublingual tablets, buprenorphine 16 mg, or placebo given daily for four 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 percent and 20.7 percent, respectively) than in the placebo group (5.8 percent,  $p < 0.001$  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.

### **Summary**

Buprenorphine products are effective therapies for the treatment of opiate dependence disorders. Patients with severe opiate dependence may be considered for methadone therapy.

### **References**

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