# Managing Opioid Addiction with Buprenorphine

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**Legislation has enabled physicians to treat opioid-dependent patients with an office-based maintenance program using buprenorphine, a partial mu-opioid receptor agonist. Clinical studies indicate buprenorphine effectively manages opioid addiction. Buprenorphine is more effective than placebo for managing opioid addiction but may not be superior to methadone if high doses are needed. It is comparable to lower doses of methadone, however. Treatment phases include induction, stabilization, and maintenance. Buprenorphine therapy should be initiated at the onset of withdrawal symptoms and adjusted to address withdrawal symptoms and cravings. Advantages of buprenorphine include low abuse potential and high availability for office use. Disadvantages include high cost and possible lack of effectiveness in patients who require high methadone doses. Most family physicians are required to complete eight hours of training before they can prescribe buprenorphine for opioid addiction. (Am Fam Physician 2006;73:1573-8, 1580. Copyright © 2006 American Academy of Family Physicians.)**

▶ **Patient information:** A handout on buprenorphine, written by the authors of this article, is provided on page 1580.

▶ **See related editorial on page 1513.**

An estimated 898,000 adults in the United States are opioid dependent.[1] Treating opioid dependence as a chronic disorder improves outcomes,[2] and opioid maintenance is the most effective way to decrease illicit use in patients who are addicted to opioids.[3] Methadone has been the treatment of choice in the United States; however, methadone maintenance programs typically have stringent entrance criteria, long waiting lists, and primarily are located in urban areas. Only 14 percent of patients who are addicted to opioids are treated in traditional methadone clinics.[4] Research from the 1970s demonstrated that the analgesic buprenorphine (Subutex), a partial mu-opioid receptor agonist, may effectively treat patients with heroin addiction.[5]

The Drug Addiction Treatment Act of 2000 enabled physicians to provide office-based treatment for opioid addiction.[6] This act allows physicians to prescribe Schedule III, IV, or V "narcotic" medications that are approved by the U.S. Food and Drug Administration (FDA) for patients with narcotic-use disorders. In 2002, the FDA approved buprenorphine and combination buprenorphine/naloxone (Suboxone) to manage opioid dependence *(Table 1)*. Both forms are Schedule III medications.

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## Pharmacology

Buprenorphine primarily affects the mu-opioid receptor, where it acts as a partial agonist; therefore, receptor activation increases as the dose increases until it reaches a plateau. Full opioid agonists, such as methadone and heroin, continue to create greater receptor activation as the dose increases, without reaching a plateau. An antagonist (e.g., naloxone [Narcan]) will not produce receptor activation regardless of dosing.

Because of this partial activation, chronic opioid users are less likely to abuse buprenorphine. The drug has a high affinity for and a slow dissociation from mu-opioid receptors and can block other opioids temporarily. Because of this high affinity, buprenorphine also displaces opioids from the mu receptor, causing withdrawal in patients who have used opioids recently. Buprenorphine is absorbed through gastrointestinal and mucosal membranes; but, the oral formulation has poor bioavailability because of extensive metabolism in the gastrointestinal tract. Sublingual buprenorphine has a

**SORT: KEY RECOMMENDATIONS FOR PRACTICE**

| *Clinical recommendation* | *Evidence rating* | *References* |
|---|---|---|
| Buprenorphine (Subutex) should be used to effectively manage opioid dependence. | A | 10-14 |
| If methadone is available, it may be a more effective treatment than buprenorphine for patients with opioid addiction. | A | 16, 19 |
| Buprenorphine should be used to treat patients with human immunodeficiency virus who are opioid-dependent. | B | 24-26 |

*A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For more information about the SORT evidence rating system, see page 1495 or http://www.aafp.org/afpsort.xml.*

bioavailability ranging from 30 to 50 percent of the intravenous dose[7,8] and a maximal plasma concentration that is reached within one hour.

Buprenorphine is metabolized primarily in the liver via the cytochrome P450. The majority of buprenorphine and its metabolites are excreted in the feces—less than 30 percent are eliminated in the urine.[9] The mean plasma elimination half-life is 37 hours.[10]

## Clinical Trials

One systematic review[11] showed that buprenorphine was more effective than placebo for opioid maintenance. In a double-blind, randomized study[12] that examined the effectiveness of buprenorphine, 150 patients were randomized to receive 2 mg of buprenorphine daily, 8 mg of buprenorphine daily, or placebo. After six days, participants could request a change in treatment groups. After two weeks, the patients treated with buprenorphine remained on the initial dosage longer, made fewer requests for group changes, used less illicit opioids, and reported better management of withdrawal symptoms compared with placebo. Three other studies[13-15] compared buprenorphine (alone and with naloxone) with placebo. The studies showed that buprenorphine increased program retention, decreased illicit opioid use, and decreased reported cravings compared with placebo. A systematic review[16] confirmed that buprenorphine is more effective in treatment retention than placebo; however, higher doses are needed to suppress heroin use compared with placebo.

Multiple clinical trials have compared buprenorphine with methadone for opioid maintenance. Most studies have shown that buprenorphine (less than 40 mg) is as effective as low-dose methadone (less than 40 mg).[17,18] High-dose methadone (greater than 60 mg) may be more effective than buprenorphine, however. A meta-analysis[18] of five studies that compared the two therapies showed that 8 to 12 mg of buprenorphine is not as effective as 50 to 80 mg of methadone.[19] A 2004 Cochrane review[16] confirmed these findings. Therefore, patients requiring higher methadone doses may not be good candidates for buprenorphine. *Table 2* compares buprenorphine and methadone.

TABLE 1
**Available Buprenorphine Formulations**

| *Medication* | *Indication* | *Description* | *Dose* |
|---|---|---|---|
| Buprenorphine tablet (Subutex) | Opioid maintenance and detoxification | White oval tablet | 2 or 8 mg SL |
| Combination buprenorphine/naloxone (Suboxone) in a 4:1 ratio | Opioid maintenance and detoxification | Orange hexagonal tablet | 2/0.5 and 8/2 mg SL |
| Buprenorphine injection | Pain management | Liquid | 0.3 mg per mL IV or IM |

*SL = sublingual; IV = intravenous; IM = intramuscular.*

TABLE 2
**Buprenorphine vs. Methadone**

| |
|---|
| **Advantages of buprenorphine (Subutex)** |
| Higher doses have lower risk of toxicity. |
| Potentially effective at less than recommended daily dosage. |
| Withdrawal symptoms are less severe after discontinuation. |
| Less abuse potential |
| More accessible for office-based treatment programs |
| **Advantages of methadone** |
| Lower cost |
| More effective in patients with higher tolerances |
| Treatment retention rates are higher. |

## Safety

Buprenorphine treatment has been studied in more than 5,000 patients in the United States and in many more patients worldwide.[18] Common side effects associated with buprenorphine include constipation, urinary retention, and sedation.[9] Mild respiratory depression is possible, and naloxone may not reverse this effect because of buprenorphine's affinity for and slow dissociation from the mu receptor.

In some case reports,[20] patients overdosed on buprenorphine and benzodiazepines. All of these overdoses involved patients who had injected dissolved buprenorphine tablets with benzodiazepines. Although there are no reports of oral or sublingual buprenorphine overdoses, physicians should be cautious when prescribing buprenorphine for patients with a history of benzodiazepine abuse. Abuse is less likely with combined buprenorphine/naloxone. Naloxone has poor oral absorption but, when injected, it antagonizes opioid effects; therefore, patients dependent on opioids are less likely to crush and inject this preparation.[21]

Because buprenorphine is metabolized primarily through the cytochrome P450 pathway, it could interact with medications that induce or inhibit this pathway *(Table 3)*. Physicians should closely monitor patients taking these medications.

## Special Considerations

Special considerations may be necessary before initiating treatment for opioid addiction in some circumstances, including when a patient is pregnant or nursing and when a patient has certain health conditions.

### PREGNANCY AND NURSING

Infants exposed to opioids in utero will show signs of withdrawal after birth. Methadone maintenance has been shown to improve outcomes in pregnant women who are dependent on opioids.[22] Published literature suggests that buprenorphine maintenance produces less intense withdrawal symptoms in newborns than methadone therapy.[23] Currently, buprenorphine is a pregnancy category C drug, and methadone (category B) is appropriate for pregnant patients. If methadone is unavailable and buprenorphine is necessary, buprenorphine without naloxone is appropriate after the physician explains the risks and benefits of the therapy to the patient. Buprenorphine is expressed in breast milk,[24] but because gastrointestinal uptake of buprenorphine is low, it is not clear whether nursing should be discouraged.

### HIV TREATMENT

Human immunodeficiency virus (HIV) is common in patients with opioid dependence;

TABLE 3
**Inducers and Inhibitors of the Cytochrome P450 Pathway**

| |
|---|
| **Inducers** |
| Carbamazepine (Tegretol) |
| Phenytoin (Dilantin) |
| Phenobarbital |
| Reverse transcriptase inhibitors |
| Rifampin (Rifadin) |
| **Inhibitors** |
| Azole antifungals |
| Macrolide antibiotics |
| Protease inhibitors |

NOTE: *Cytochrome P450 inhibitors increase the effect of buprenorphine, whereas cytochrome P450 inducers decrease the effect.*

therefore, these patients may be undergoing highly active antiretroviral therapy (HAART). Two studies[25,26] examined buprenorphine treatment for patients dependent on opioids who were undergoing HAART. The authors concluded that patients receiving buprenorphine treatment were more likely to adhere to the HAART regimen than those not receiving buprenorphine.[25] The study also demonstrated that buprenorphine did not affect patients' virologic response to HAART.[26]

An in vitro study[27] examining the effects of three protease inhibitors (ritonavir [Norvir], indinavir [Crixivan], and saquinavir [Fortovase]) showed that they potentially can interfere with buprenorphine metabolized through cytochrome P450. Physicians may need to decrease the buprenorphine dose for patients also taking protease inhibitors.

#### HEPATITIS

Hepatitis B and C also are commonly associated with opioid dependence. Physicians should monitor the liver function of patients with hepatitis who are taking buprenorphine, because the drug is metabolized in the liver. Case reports[28] have shown that intravenous buprenorphine may cause significant liver damage in patients with hepatitis C.

## Dosing

Management of opioid addiction with buprenorphine can be divided into three phases: induction, stabilization, and maintenance.[29] The induction phase includes the initial transition from illicit opioid use to buprenorphine and typically lasts three to seven days. Patient education is important during this phase and should emphasize the risk of precipitating withdrawal if buprenorphine is initiated too soon after opioid use. Generally, buprenorphine should be initiated 12 to 24 hours after short-acting opioid use and 24 to 48 hours after long-acting opioid use. Most patients should use combination buprenorphine/naloxone tablets. Pregnant women who are candidates for buprenorphine, and some patients using long-acting opioids (e.g., methadone), should use the buprenorphine-only formulation. In the latter case, the methadone dose should be less than 30 mg,[21] and the patient should switch to the combination tablet after several days.

**Common side effects associated with buprenorphine include constipation, urinary retention, and sedation.**

TABLE 4
**Nonopioid Treatments for Opioid Withdrawal Symptoms**

| *Symptom* | *Medication* |
|---|---|
| Abdominal cramps | Dicyclomine (Bentyl) |
| Agitation | Hydroxyzine (Atarax) |
| Diarrhea | Loperamide (Imodium) |
| Insomnia | Trazodone (Desyrel) |
| Muscle aches | Ibuprofen (Motrin) |
| Withdrawal | Clonidine (Catapres) |

After the patient presents with opioid withdrawal symptoms, the initial doses should be administered under physician observation (4/1 mg buprenorphine/naloxone or 2 mg buprenorphine if the patient is dependent on a long-acting opioid). The physician should monitor the patient for precipitated withdrawal and excessive side effects (e.g., sedation). If the patient continues to exhibit signs of opioid withdrawal after two hours, another 4/1 mg dose of buprenorphine/naloxone should be administered. Patients who are dependent on long-acting opioids should receive 2 mg buprenorphine every one to two hours. The maximum recommended first-day dosage of buprenorphine is 8 to 12 mg. If the patient continues to show signs of withdrawal, the physician may administer adjunctive nonopioid and symptomatic treatments *(Table 4)*.

On the second day of induction, the physician should determine the extent of withdrawal. If buprenorphine was used on the initial day, buprenorphine/naloxone should be used for the remainder of the induction period. If the patient reports no withdrawal symptoms, the total dosage from the first day should be repeated and the patient should remain on that daily dose. If the patient shows signs of withdrawal, the total dosage from the first day plus 4/1 mg

buprenorphine/naloxone should be administered. Subsequent dose increases of 2/0.5 or 4/1 mg may be administered until the total daily buprenorphine dose reaches 16 mg.

During the remainder of the induction phase, the procedure should be repeated to a maximum daily dosage of 32/8 mg by the end of the first week. If the patient continues to experience opioid withdrawal, illicit opioid use should be suspected.

The stabilization phase generally lasts one to two months and includes medication adjustments to establish the minimum dosage required to eliminate withdrawal symptoms, reduce opioid cravings, and minimize side effects. For most patients, the minimum daily dosage of buprenorphine/naloxone is 12/3 to 24/6 mg. The physician should have frequent contact with the patient during this period to facilitate dose adjustments and enhance compliance. The need for further psychosocial addiction treatment also should be assessed.

The maintenance phase is indefinite and should be determined for each patient individually. During this phase, the physician should continue to monitor the patient for illicit drug use, cravings, and triggers to relapse. Ensuring that psychosocial issues are addressed through the physician's office, other counseling, or self-help mechanisms, also is important.

**Under federal law, only qualified physicians can prescribe buprenorphine for opioid addiction.**

During treatment, physicians should anticipate and define a plan for relapse. This may include increased counseling or adjusting buprenorphine dosing.

## Formulations and Costs

A list of available formulations is shown in *Table 1*. A 15-day supply of 2/0.5 mg buprenorphine/naloxone tablets costs approximately $100 from a retail pharmacy. A 30-day supply of methadone costs approximately $30, not including counseling.[21]

## Regulation

Under federal law, only qualified physicians can prescribe buprenorphine for opioid addiction. Physicians are required to have an active U.S. Drug Enforcement Agency registration and a waiver to prescribe buprenorphine. Waivers permit a physician to treat up to 30 patients. Most physicians can qualify after completing eight hours of approved training. *Table 5* summarizes the qualification criteria.[29]

TABLE 5
**Requirements for Qualifying to Prescribe Buprenorphine**

| |
|---|
| Licensed under state law |
| Has the capacity to refer patients for counseling and ancillary services |
| Meets one of the following criteria: |
| Board certified in addiction psychiatry |
| Certified in addiction medicine from the ASAM |
| Board certified in addiction medicine from the AOA |
| Completed at least eight hours of training in the treatment and management of opioid addiction provided by an approved association |
| Participated in clinical trials leading to the approval of buprenorphine (Subutex) |
| Training or experience approved by the physician's state licensing board or the U.S. Secretary of Health and Human Services |

*ASAM = American Society of Addiction Medicine; AOA = American Osteopathic Association.*

*Information from reference 29.*

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