

SORT: KEY RECOMMENDATIONS FOR PRACTICE

<i>Clinical recommendation</i>	<i>Evidence rating</i>	<i>References</i>
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 review¹¹ showed that buprenorphine was more effective than placebo for opioid maintenance. In a double-blind, randomized study¹² 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 studies¹³⁻¹⁵ 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 review¹⁶ 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-analysis¹⁸ 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 review¹⁶ 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**

<i>Medication</i>	<i>Indication</i>	<i>Description</i>	<i>Dose</i>
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 study²⁷ 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 reports²⁸ 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

TABLE 4
Nonopioid Treatments for Opioid Withdrawal Symptoms

<i>Symptom</i>	<i>Medication</i>
Abdominal cramps	Dicyclomine (Bentyl)
Agitation	Hydroxyzine (Atarax)
Diarrhea	Loperamide (Imodium)
Insomnia	Trazodone (Desyrel)
Muscle aches	Ibuprofen (Motrin)
Withdrawal	Clonidine (Catapres)

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.

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

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

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.

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

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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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REFERENCES

1. United States Office of National Drug Control Policy. The president's national drug control strategy, 2002. Accessed online May 25, 2005, at: <http://www.whitehousedrugpolicy.gov/publications/policy/03ndcs/index.html>.
2. McLellan AT, Lewis DC, O'Brien CP, Kleber HD. Drug dependence, a chronic medical illness: implications for treatment, insurance, and outcomes evaluation. *JAMA* 2000;284:1689-95.
3. Mattick RP, Breen C, Kimber J, Davoli M. Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. *Cochrane Database Syst Rev* 2003;(2):CD002209.
4. Rounsaville BJ, Kosten TR. Treatment for opioid dependence: quality and access. *JAMA* 2000;283:1337-9.
5. Jasinski DR, Pevnick JS, Griffith JD. Human pharmacology and abuse potential of the analgesic buprenorphine: a potential agent for treating narcotic addiction. *Arch Gen Psychiatry* 1978;35:501-16.
6. Drug Addiction Treatment Act of 2000, 21 USC, §3501 (2000). Accessed online, October 12, 2005, at: <http://buprenorphine.samhsa.gov/data.html>.
7. Mendelson J, Upton RA, Everhart ET, Jacob P III, Jones RT. Bioavailability of sublingual buprenorphine. *J Clin Pharmacol* 1997;37:31-7.
8. Kuhlman JJ Jr, Lalani S, Maglullo J Jr, Levine B, Darwin WD. Human Pharmacokinetics of intravenous, sublingual, and buccal buprenorphine. *J Anal Toxicol* 1996;20:369-78.
9. Cone EJ, Gorodetzky CW, Yousefnejad D, Buchwald WF, Johnson RE. The metabolism and excretion of buprenorphine in humans. *Drug Metab Dispos* 1984;12:577-81.
10. Suboxone Web site. Learn more about Suboxone. Accessed online May 25, 2005, at: <http://www.suboxone.com>.
11. Gowling L, Ali R, White J. Buprenorphine for the management of opioid withdrawal. *Cochrane Database Syst Rev* 2004;(4):CD002025.
12. Johnson RE, Eissenberg T, Stitzer ML, Strain EC, Liebson IA, Bigelow GE. A placebo controlled clinical trial of buprenorphine as a treatment for opioid dependence. *Drug Alcohol Depend* 1995;40:17-25.
13. Ling W, Charuvastra C, Collins JF, Batki S, Brown LS Jr, Kintaudi P, et al. Buprenorphine maintenance treatment of opiate dependence: a multicenter, randomized clinical trial. *Addiction* 1998;93:475-86.
14. Krook AL, Brors O, Dahlberg J, Grouff K, Magnus P, Roysamb E, et al. A placebo-controlled study of high dose buprenorphine in opiate dependents waiting for medication-assisted rehabilitation in Oslo, Norway. *Addiction* 2002;97:533-42.
15. Fudala PJ, Bridge TP, Herbert S, Williford WO, Chiang CN, Jones K, et al. Office-based treatment of opiate addiction with a sublingual-tablet formulation of buprenorphine and naloxone. *N Engl J Med* 2003;349:949-58.
16. Mattick RP, Breen C, Kimber J, Breen C, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *Cochrane Database Syst Rev* 2003;(2):CD002207.
17. Kosten TR, Schottenfeld R, Ziedonis D, Falcioni J. Buprenorphine versus methadone for opioid dependence. *J Nerv Ment Dis* 1993;181:358-64.
18. Schottenfeld RS, Pakes JR, Oliveto A, Ziedonis D, Kosten TR. Buprenorphine vs methadone maintenance treatment for concurrent opioid dependence and cocaine abuse. *Arch Gen Psychiatry* 1997;54:713-20.
19. Barnett PG, Rodgers JH, Bloch DA. A meta-analysis comparing buprenorphine to methadone for treatment of opiate dependence. *Addiction* 2001;96:683-90.
20. Obadia Y, Perrin V, Feroni I, Vlahov D, Moatti JP. Injecting misuse of buprenorphine among French drug users. *Addiction* 2001;96:267-72.
21. Buprenorphine: an alternative to methadone. *Medical Letter Drugs Ther* 2003;45:13-5.
22. Connaughton JF, Reeser D, Schut J, Finnegan LP. Perinatal addiction: outcome and management. *Am J Obstet Gynecol* 1977;129:679-86.
23. Johnson RE, Jones HE, Fischer G. Use of buprenorphine in pregnancy: patient management and effects on the neonate. *Drug Alcohol Depend* 2003;70(suppl):S87-101.
24. Johnson RE, Jones HE, Jasinski DR, Svikis DS, Haug NA, Jansson LM, et al. Buprenorphine treatment of pregnant opioid-dependent women: maternal and neonatal outcomes. *Drug Alcohol Depend* 2001;63:97-103.
25. Moatti JP, Carrieri MP, Spire B, Gastaut JA, Cassuto JP, Moreau J, for the Manif 2000 Study Group. Adherence to HAART in French HIV-infected injecting drug users: the contribution of buprenorphine drug maintenance treatment. *AIDS* 2000;14:151-5.
26. Carrieri MP, Vlahov D, Dellamonica P, Gallais H, Lepeu G, Spire B, et al., for the Manif 2000 Study Group. Use of buprenorphine in HIV-infected injection drug users: negligible impact on virologic response to HAART. *Drug Alcohol Depend* 2000;60:51-4.
27. Iribarne C, Berthou F, Carlhant D, Dreano Y, Picart D, Lohezic F, et al. Inhibition of methadone and buprenorphine N-dealkylations by three HIV-1 protease inhibitors. *Drug Metab Dispos* 1998;26:257-60.
28. Berson A, Gervais A, Cazals D, Boyer N, Durand F, Bernuau J, et al. Hepatitis after intravenous buprenorphine misuse in heroin addicts. *J Hepatol* 2001;34:346-50.
29. McNicholas L. Clinical guidelines for the use of buprenorphine in the treatment of opioid addiction. Rockville, Md.: U.S. Department of Health and Human Services, Substance Abuse and Mental Health Services Administration, Center for Substance Abuse Treatment, 2004. Treatment improvement protocol (TIPS) series.