

# The Medical Letter®

On Drugs and Therapeutics

www.medicalletter.org

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Published by The Medical Letter, Inc. • 1000 Main Street, New Rochelle, NY 10801 • A Nonprofit Publication

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Vol. 45 (W1150A)  
February 17, 2003

REPRODUCED FOR  
ONLINE USERS

## BUPRENORPHINE: AN ALTERNATIVE TO METHADONE

The FDA has approved the marketing of buprenorphine in sublingual tablets (Reckitt Benckiser) both alone (*Subutex*) and with naloxone (*Suboxone*) for treatment of opioid dependence. Previously available only for parenteral use in treatment of pain (*Buprenex*, and others), it offers an alternative to methadone (*Dolophine*, and others), which is now often abused (New York Times, February 9, 2003; page 1). As a schedule III narcotic, buprenorphine will be subject to fewer prescribing restrictions than a schedule II drug such as methadone (MJ Kreek and FJ Vocci, *J Subst Abuse Treat* 2002; 23:93).

**MECHANISM OF ACTION** — Buprenorphine is a partial opioid agonist at mu receptors. In non-dependent subjects, it produces typical opioid agonist effects such as analgesia, sedation, nausea and dizziness, but these reach a maximum ("ceiling") in most patients with sublingual doses of 24 to 32 mg. In patients physically dependent on mu-receptor agonists such as morphine or heroin, buprenorphine usually prevents symptoms of withdrawal, but in high doses it can act as an antagonist and precipitate withdrawal symptoms. Naloxone (*Narcan*) is an opioid antagonist; given IV, it reverses the effects of most opioids (Medical Letter 2002; 44:22). Taken orally, it is poorly absorbed and generally has no clinical effects. Its presence in sublingual combination tablets with buprenorphine is intended to discourage intravenous abuse of buprenorphine by opioid-dependent patients.

**REGULATORY REQUIREMENTS** — The Drug Addiction Treatment Act of 2000 permits office-based prescribing of Schedule III, IV and V drugs approved for treatment of opioid dependence (currently only buprenorphine fits this description) by qualified physicians who are certified in addiction medicine or addiction psychiatry, or have completed at least 8 hours of authorized training, or have participated in a clinical trial ([www.suboxone.com](http://www.suboxone.com)). Prescribers must register with the Substance Abuse and Mental Health Services Administration ([www.dpt.samhsa.gov](http://www.dpt.samhsa.gov)), and each physician or group practice is permitted to treat a maximum of 30 patients with the drug at one time.

**PHARMACOLOGY** — Naloxone has no effect on absorption of buprenorphine. Serum concentrations of buprenorphine reach a peak 30-60 minutes after sublingual administration. The drug is metabolized in the liver primarily by CYP3A4, and is excreted mostly in feces and partly in urine. Its mean elimination half-life is 37 hours.

**CLINICAL STUDIES** — The effectiveness of various regimens of sublingual buprenorphine in treating withdrawal from opioid dependence and in short-term (up to 1 year) maintenance has been established in randomized controlled trials (L Gowing et al, *Cochrane Database Syst*

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Rev 2002; 2:CD002025; RD Mattick et al, Cochrane Database Syst Rev 2002; 4:CD002207). In one 17-week study in 270 patients, sublingual buprenorphine 3 times a week was about as effective for maintenance as methadone or levomethadyl acetate (LAAM), a long-acting congener of methadone (RE Johnson et al, N Engl J Med 2000; 343:1290). A 2-year follow-up of more than 900 opioid-dependent patients treated with *Subutex* tablets (mean 8 mg/day) by general practitioners in France found that, in general, these patients remained on treatment and showed improvement in social status and a decrease in drug abuse (A Fhima et al, Ann Med Interne (Paris) 2001; 152 suppl 3:1S26). The major limitation of buprenorphine in the management of heroin addiction is its partial agonist effect; the maximum effective dose of buprenorphine (24-32 mg) is equivalent to only 60-70 mg of oral methadone.

**ADVERSE EFFECTS** — Buprenorphine can cause typical opioid effects such as sedation, nausea, itching and constipation, but in high doses it can cause withdrawal symptoms such as sweating, flu-like symptoms, abdominal pain, insomnia and mood swings in patients dependent on opioids. Because it is a partial agonist with a long half-life due to prolonged occupancy of the mu receptor, withdrawal symptoms are relatively mild when buprenorphine itself is discontinued. Respiratory depression can occur with overdosage, but life-threatening respiratory depression is much less likely than with a pure mu agonist such as heroin or methadone, unless another CNS depressant is taken at the same time. Most deaths related to buprenorphine have been caused by injection of both dissolved buprenorphine tablets and a benzodiazepine. Because of buprenorphine's prolonged occupancy of the mu receptor, naloxone may not reverse respiratory depression when it occurs.

A broad spectrum of hepatic abnormalities has been reported in patients taking buprenorphine for opioid addiction; in these substance-abusing patients with high rates of viral hepatitis and frequent use of hepatotoxic drugs, cause and effect have been difficult to establish. Allergic reactions, including angioneurotic edema and anaphylaxis, have been reported. Few data are available on use of the drug during pregnancy, but there is no reason to believe it would cause more problems than methadone or any other opioid. As with methadone, a neonatal abstinence syndrome can occur. Buprenorphine is secreted in breast milk; nursing is contraindicated.

**DRUG INTERACTIONS** — Potent 3A4 inhibitors such as ketoconazole (*Nizoral*, and others), erythromycin and HIV protease inhibitors can cause substantial increases in plasma concentrations of buprenorphine.

**DOSAGE AND COST** — Both *Subutex* and *Suboxone* are supplied as 2- and 8-mg tablets for sublingual use; *Suboxone* tablets also contain 0.5 and 2 mg of naloxone. Chewing or swallowing the tablets reduces bioavailability. Patients transferred from methadone maintenance should have methadone doses reduced to  $\leq 30$  mg before switching. Buprenorphine should not be started until at least 4 hours after last use of a short-acting opioid, or at least 24 hours after a long-acting one such as methadone, preferably after the patient experiences early withdrawal symptoms. Induction dosing should begin with 2 or 4 mg on day 1, which can be repeated q2-4h if withdrawal symptoms subside and then reappear (max. 8 mg on first day), and generally should be titrated in 2-4 mg increments to 12 to 16 mg on day 2. Higher-than-necessary doses during induction may cause opioid-withdrawal symptoms. Most patients can be stabilized on 8-32 mg/day. Alternate-day and three-times-a-week schedules have also been used effectively. According to the manufacturer, *Suboxone* 16 mg/day costs \$287.50 for a month's supply, compared to less than \$30 for a month's supply of methadone at usual doses. *Subutex* is not yet available.

**CONCLUSION** — Buprenorphine taken alone as *Subutex* or with naloxone as *Suboxone* appears to be an effective alternative to methadone for both opioid detoxification and maintenance treatment of opioid dependence. It appears to be safer than methadone, with a lower risk of illicit use, but may not be effective for patients maintained on high doses of methadone. Buprenorphine's availability for office-based treatment should make it more accessible than methadone, but its high cost may be a deterrent.

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