National PBM Drug Monograph

Sublingual Buprenorphine/Naloxone and Buprenorphine (SUBOXONE and SUBUTEX)

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VHA Pharmacy Benefits Management Strategic Health Care Group and the Medical Advisory Panel

Executive Summary

Sublingual buprenorphine/naloxone and buprenorphine are the first products to become available in the U.S. for office-based treatment of opioid dependence under the Drug Addiction Treatment Act of 2000 (DATA 2000). This law allows specially qualified physicians to prescribe Schedule III to V drugs for treatment of opioid dependence in an office setting. The main objective of this law was to expand access to treatment for opioid dependence by incorporating the management of opioid dependence into mainstream primary care.

Buprenorphine/naloxone and buprenorphine are generally not superior to methadone as maintenance of opioid dependence but they are more expensive. Buprenorphine/naloxone acquisition costs are 15 times higher at approximated methadone-equivalent doses and, using simulated pharmacoeconomic modeling, cost-effectiveness of buprenorphine/naloxone or buprenorphine is lower than that for methadone under almost all economic scenarios. An empirical cost-effectiveness analysis of buprenorphine relative to methadone will need to take into account several population-related differences and the fact that the two drugs are not complete therapeutic alternatives for each other.

Buprenorphine/naloxone and buprenorphine may be safer than other OATs; however, further evaluation and experience are needed to determine their relative safety and to characterize the effects of buprenorphine on the liver.

In general, methadone should remain the substitution treatment of choice for opioid dependence. Buprenorphine may play a valuable role in the substitution treatment of opioid dependence when other OATs are not available, not accessible in a timely fashion, do not achieve desired clinical outcomes, or cannot be tolerated; or when the patient has difficulty making required visits at OAT clinics.

Sublingual tablets of buprenorphine or buprenorphine/naloxone should not be used for treatment of pain in the absence of DSM-IV criteria of opioid dependence.

Introduction

In the VA, as is true in the U.S., the legal restrictions placed on opioid agonist treatment (OAT) centers (a.k.a. methadone maintenance clinics) have resulted in a shortage of and limited access to OAT centers for opioid-dependent individuals. Other factors have contributed to restricting access to OAT centers as well, such as the stigma associated with methadone treatment and inability of many patients to comply with the required daily visits for methadone treatment. Although the number of VA OAT centers has

increased in the past several years, many geographical areas still remain without OAT clinics. The use of methadone in primary care, referred to as methadone medical maintenance, has been successful in a pilot program.[1] This potential alternative for expanding access to methadone, however, is still in its infancy and must overcome many legal barriers before it can be fully implemented.

Buprenorphine is a Schedule III partial opioid agonist that was approved by the FDA for the treatment of opioid dependence on October 8th, 2002. When buprenorphine and the combination buprenorphine/naloxone products were launched in early January 2003, they became the first agents available in the U.S. for office-based treatment of opioid dependence under the Drug Addiction Treatment Act of 2000 (DATA 2000). This law allows specially qualified physicians to prescribe Schedule III to V drugs for treatment of opioid dependence in an office setting. The main objective of this law was to expand access to treatment for opioid dependence by incorporating the management of opioid dependence into mainstream primary care. DATA 2000 eliminated many of the legal constraints that have suppressed the delivery of OAT in the past. Treatment with buprenorphine can be provided in a less stigmatizing environment and requires less frequent visits. Patients will be able to receive treatment for other related medical problems at clinic visits and obtain drug at a local pharmacy instead of an OAT clinic. The introduction of the two buprenorphine products in the U.S. represented a paradigm shift in the treatment of opioid dependence. It was the first major viable attempt to increase the accessibility, convenience, and acceptability of OAT since the introduction of methadone clinics.

The purpose of this monograph update was to identify any new evidence that might support modification of the criteria for use of buprenorphine in the VA and to provide a brief review of current literature. This monograph update mainly reviews additional data on buprenorphine published since 2002, although previous articles have also been added for relevant topics. Since preparation of the previous monograph on buprenorphine, substantially more information has been published regarding the use of buprenorphine for medically supervised withdrawal (detoxification).

Pharmacology/Pharmacokinetics

Pharmacology

Buprenorphine is a partial agonist at the mu-opioid receptor and an antagonist at the kappa-opioid receptor. Buprenorphine produces weaker opioid agonist effects than methadone and its opioid agonist activity is limited by a ceiling effect. Based on subjective and physiologic responses in healthy volunteers, the ceiling effect generally occurs around 16 mg.[2] It produces less respiratory depression than full opioid agonists, which lack a ceiling effect. Buprenorphine has a greater affinity for and a slower dissociation from the mu-opioid receptor than full agonist opioids and may block or displace other opioid agonists from receptor sites.

While sublingual buprenorphine is used therapeutically to prevent withdrawal symptoms, it can also potentially precipitate withdrawal in an opioid-dependent individual maintained on a sufficient dose of opioid with stronger agonist activity. The precipitated withdrawal syndrome is difficult to reverse because of the high affinity of buprenorphine for the opioid receptor and giving additional doses of opioids other than buprenorphine is

unlikely to ameliorate the withdrawal symptoms. If buprenorphine-precipitated withdrawal occurs, symptomatic treatment would be indicated.

Buprenorphine has a lower potential to cause physical dependence and is easier to discontinue at the end of treatment than full opioid agonists.

Buprenorphine also lacks psychotomimetic effects.

Naloxone is an antagonist at the mu-opioid receptor, and was added to buprenorphine to discourage parenteral abuse of buprenorphine.[3] If given sublingually to opioid-dependent individuals after the opioid agonist effects have abated, naloxone is unlikely to produce clinically relevant effects. However, if sublingual naloxone is given to these individuals before the agonist effects of the opioid have diminished, precipitated withdrawal may occur. Buprenorphine/naloxone, when misused intravenously, is highly likely to precipitate intense withdrawal symptoms in individuals dependent on other opioid agonists. The addition of naloxone may reduce (but not totally eliminate) injection abuse of buprenorphine and experts generally agree that buprenorphine/naloxone is the formulation of choice in most situations.

Pharmacokinetics

Absorption

There is wide interpatient variability in the sublingual absorption of buprenorphine and naloxone, but low intrapatient variability. Both C_{max} and AUC for buprenorphine increase linearly as dose is increased, but not in a dose-proportional fashion.

Earlier studies used a sublingual ethanolic solution rather than tablets. The bioavailability of tablets has varied widely between studies. Relative to the solution, estimates of the bioavailability of the tablets has varied widely among studies, ranging from 40% to over 70%.[4-5]

Relative bioavailability may depend on treatment duration and the type of sublingual tablet formulation.[6] Differences in bioavailability between the tablet and solution formulations may decrease with repeated dosing, such that the buprenorphine/naloxone tablets and solution have similar bioavailabilities after 2 weeks of stable dosing.[6] The combination buprenorphine/naloxone formulation has been shown to have either greater[6] or similar[7] bioavailability as compared with buprenorphine alone. There may be considerable inter-individual variability in bioavailability of the tablet relative to the solution.[8] One study did not show differences in physiologic, objective, or subjective opioid effects despite showing lower bioavailability (71%) of the tablet relative to the solution.[9] The differences in bioavailability and clinical correlates between the tablets and solution, as well as the impact of sublingual formulation and treatment duration on relative bioavailability, need to be taken into account when evaluating studies. The variability in reported bioavailabilities also make it difficult to extrapolate sublingual tablet doses from the sublingual solution doses used in studies. In clinical practice, the high variability in bioavailability necessitates individualized titration of doses.

Naloxone has very low bioavailability when taken orally or sublingually, but plasma concentrations are detectable.

Distribution, Metabolism, and Elimination

The other pharmacokinetic properties of buprenorphine and naloxone are shown in Table 1.

Table 1 Pharmacokinetic properties of buprenorphine and naloxone

	Buprenorphine	Naloxone
Protein Binding	96% (alpha and beta globulin)	45% (albumin)
Metabolism	N-dealkylation via CYP-3A4 to norbuprenorphine (an active metabolite) Glucuronidation	Direct glucuronidation to naloxone 3-glucuronide N-dealkylation Reduction of 6-oxo group
Elimination	Renal and fecal	Hepatic
Half-life (h)	37	1.1

FDA Approved Indication(s)

Treatment of opioid dependence. Only the sublingual buprenorphine tablet formulations have been authorized to be used for management of opioid dependence.

The injectable formulation of buprenorphine, which is FDA-approved for the treatment of moderate to severe pain, is not a legally authorized treatment for opioid dependence and must not be used for such purpose under any circumstances.

Medically supervised withdrawal (detoxification). There are no FDA-approved dosing recommendations for the use of sublingual buprenorphine/naloxone and buprenorphine in medically supervised withdrawal; however, detoxification is considered to be part of the treatment of opioid dependence.

Off-label Uses

Pain management. The analgesic efficacy and safety of sublingual buprenorphine have not been evaluated in patients who have opioid dependence (DSM-IV diagnosis) and a concurrent pain syndrome.

There are indirect data suggesting that high-dose sublingual buprenorphine might be useful for chronic pain. A multicenter postmarketing surveillance study in India documented that 2063 (37.2%) of 5551 subjects undergoing treatment with sublingual buprenorphine (mean daily dose 2.9 mg, range 0.4 to 36 mg) for opioid dependence (diagnostic criteria not specified) reported relief from pain as a subjective symptom.[10]

In one poor-quality open-label observational study in 95 consecutive patients with chronic pain syndrome (8% with DSM-IV-TR diagnosis of opioid dependence), sublingual buprenorphine/naloxone or buprenorphine, titrated to pain control and opioid abstinence symptoms (mean 8 mg, range 4 to 16 mg, in divided daily doses for a mean of 8.8 months), relieved chronic noncancer pain to a moderate or substantial degree in 86% of the patients.[11] These patients were refractory to long-term opioid analgesic therapy and had been referred for medically supervised withdrawal from opioid therapy. The authors

noted anecdotally that, although pain relief was often only fair, patients reported improvements in tolerance to pain, mood, and functional capacity after buprenorphine therapy. There are no well-designed trials of the use of high-dose sublingual buprenorphine for relieving chronic pain syndromes in patients with a concurrent diagnosis of opioid dependence (DSM-IV).

In patients without opioid dependence (DSM-IV), sublingual buprenorphine in doses much smaller than those used for opioid maintenance therapy has been shown to be effective for acute post-operative pain.[12-16] Sublingual buprenorphine has also been demonstrated to relieve chronic pain to a degree not statistically different from phenytoin in one small double-blind RCT[17] and less effectively than tramadol (100 mg orally every 8 to 12 hours) in a randomized trial [blinding not stated][18]).

The doses used for opioid maintenance therapy (minimum 2 mg) are five to ten times higher than those evaluated for acute pain (0.2 to 0.4 mg per dose).[12-16] The dose of sublingual buprenorphine for opioid dependence is generally higher than those used for chronic pain; however, the lower total daily doses of sublingual buprenorphine used for opioid dependence overlap with the upper end of the dosing range evaluated for chronic pain (e.g., 2 to 16 mg per day vs. 0.4 to 3.2 mg per day).[17-20]

In the U.S., buprenorphine sublingual tablets in strengths lower than 2 mg are not available and the tablets are not scored. The analgesic effects of the higher and once daily doses of sublingual buprenorphine recommended in opioid maintenance therapy have not been evaluated. Patients who require therapy for acute or chronic pain and who are not being treated for addiction should be managed using standard analgesic treatments.

In addition, there may be physiologic and pharmacodynamic factors as well as misconceptions that complicate the management of acute pain in addictive patients on OAT, including potentially insufficient analgesic duration of maintenance OAT, tolerance, and opioid-induced hyperalgesia.[21]

Current VA National Formulary Alternatives

Office-based OAT settings. Sublingual buprenorphine/naloxone and buprenorphine are currently the only products available for medically supervised withdrawal and maintenance treatment of opioid dependence in a nonspecialty clinic setting. Naltrexone, an opioid antagonist, is indicated for a different purpose (i.e., maintenance of opioid abstinence by blocking opioid receptors) in the treatment of opioid dependence and is not an alternative to sublingual buprenorphine.

In clinical studies, methadone medical maintenance in primary care has been successful for stable, rehabilitated methadone-treated patients where, over a 15-year period, 132 (83.5%) of 158 carefully selected patients remained compliant with regulations related to office-based methadone treatment.[22-24] Methadone medical maintenance in primary care is not currently a feasible option in the U.S.

Specialty OAT programs. Methadone is the only agent, other than sublingual buprenorphine/naloxone and buprenorphine, that is available for treatment of opioid dependence in licensed OAT programs. Levo-methadyl acetate (levo-alpha-acetyl methadol, LAAM) was discontinued from the U.S. market in August 2003 because of

reports of severe cardiac-related adverse events including cardiac arrhythmias and cardiac arrest.

Dosage and Administration

Buprenorphine is available as a single drug in 2- and 8-mg tablets and as a combination of buprenorphine and naloxone in 2 mg/0.5 mg and 8 mg/2 mg tablets. Buprenorphine/naloxone is recommended for induction and maintenance or when clinical use includes unsupervised administration. The buprenorphine monodrug product should be limited to patients who are pregnant or cannot tolerate naloxone (e.g., patients with a documented hypersensitivity to naloxone).

Methadone-equivalent doses of buprenorphine may be approximated by extrapolation of results from a meta-analysis by Mattick, et al. [25] Buprenorphine 6 to 12 mg appears to be similar to methadone doses between 35 and 60 mg, at least in terms of illicit drug use (positive UDS). Another systematic review suggests that buprenorphine 2 to 8 mg is less effective in retaining patients in treatment and decreasing illicit drug use than methadone doses greater than 65 mg.[26]

Buprenorphine (hereinafter referring to the buprenorphine/naloxone combination or the monodrug product unless specifically indicated as either formulation), is administered once daily. The tablets must be taken sublingually, allowing 5 to 10 minutes for the tablets to completely dissolve. Oral administration of the tablets reduces the bioavailability of the drug.

Dosing for opioid agonist substitution (maintenance) therapy

A brief summary of dosing recommendations is provided here. For more detailed instructions on dosage and administration of buprenorphine, consult appropriate references such as the *Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction* Treatment Improvement Protocol (TIP) 40 available from the Center for Substance Abuse Treatment (CSAT) (see http://buprenorphine.samhsa.gov/publications.html).

The use of buprenorphine should be part of a comprehensive treatment plan that includes psychosocial treatment modalities.

Induction

For induction, experts currently suggest using the buprenorphine/naloxone combination product and reserving the buprenorphine monodrug product for treating pregnant females or individuals with a documented intolerance or hypersensitivity to naloxone. The product information recommends using the buprenorphine monodrug product for induction then switching to the combination buprenorphine/naloxone product starting on day 3, although there is no contraindication to using the combination product for induction.

There have been no studies comparing the two products for induction. However, the buprenorphine/naloxone combination (up to 8 mg/2 mg) was shown to be safe for initiating induction during field trials for medically supervised withdrawal in patients with methadone- and benzodiazepine-negative urine drug screens.[27]

It is important to start induction with buprenorphine/naloxone (or buprenorphine alone in pregnant or naloxone-intolerant individuals) when signs of early opioid withdrawal have appeared, taking into consideration the type of opioid dependence.

Day 1

Patients physically dependent on heroin or other short-acting opioids

Initiate buprenorphine therapy at least 4 hours, preferably at least 12 to 24 hours, after the patient last used opioids or preferably when the patient exhibits definite signs of withdrawal. The maximal recommended induction dose of buprenorphine is 8 mg on day 1 (given at once or in divided doses as clinically indicated).

Patients physically dependent on methadone or other long-acting opioids

Limited controlled experience with the conversion of methadone-maintained patients to buprenorphine suggests that precipitated withdrawal symptoms are possible, particularly in patients maintained on methadone doses greater than 30 to 40 mg daily or when buprenorphine is started shortly after the last methadone dose.[28] Therefore, to avoid precipitating withdrawal symptoms when conversion from methadone or other long-acting opioid to buprenorphine, experts currently recommend that the dose of the long-acting opioid be tapered to the equivalent of methadone 30 to 40 mg daily or less and the last dose of methadone be taken at least 24 hours before starting buprenorphine.

This method is intended to reduce the likelihood of precipitated withdrawal symptoms upon transitioning to buprenorphine, and the *conversion* dose of methadone should not be considered the dose *equivalent* to a starting dose of buprenorphine. Conversion from higher doses of methadone to buprenorphine may also be possible,[29,30,31] but requires further evaluation.

The induction dose of buprenorphine should start at a minimum of 2 mg, repeating doses as needed up to 8 mg in 24 hours.

Day 2 and onward

If no serious adverse effects or evidence of withdrawal emerge within two hours of the administration of a dose, the patient is ready to move on to the next step in induction. On day 2, the dose should be advanced by 2 to 4 mg. Thereafter (day 3 and on), buprenorphine should be titrated to achieve an adequate maintenance dose.

Adjust the buprenorphine dose in increments or decrements of 2 or 4 mg per day to a level that holds the patient in treatment and suppresses opioid withdrawal effects. The recommended target dose of buprenorphine is 12 to 16 mg per day to be achieved within the first week, unless adverse effects occur. Should adverse effects occur, the dose of buprenorphine should be maintained or decreased until these adverse effects abate. If patients continue to have problems adjusting to buprenorphine (experiencing withdrawal symptoms or feeling compelled to use illicit drugs), the dosage may need to be increased more rapidly.

Physicians should attempt to achieve an adequate maintenance dose, titrated to clinical effectiveness, as quickly as possible to prevent the patient from developing undue opioid withdrawal symptoms. In some studies, gradual induction over several days led to a high

rate of dropouts during the induction period. In one study, buprenorphine 8 mg was given on day 1 and 16 mg on day 2. Induction was accomplished over 3 to 4 days depending on the target dose.[32] There have been no published trials evaluating different induction doses of buprenorphine.

Stabilization (approximately one to two months)

The induction phase is completed and the stabilization phase has begun when the patient has discontinued or markedly reduced the use of illicit drugs, is experiencing no withdrawal symptoms, is experiencing minimal or no side effects, and no longer has cravings for the drug of abuse. Dosage adjustments may still be necessary during this period. Doses may be increased in 2- to 4-mg increments per week until stabilization is achieved. The majority of patients should stabilize on doses between 12 to 16 mg, but doses can be increased up to 32 mg.

Maintenance

For induction and stabilization, once daily dosing of buprenorphine is preferable. For maintenance, once daily dosing has also usually been used; however, less frequent dosing of buprenorphine is possible due to the drug's long duration of action.

Alternate-day dosing,[33-37] thrice weekly,[38-40,41] twice weekly,[41] every-third-day,[37,40] and every-fourth-day[40] dosing of buprenorphine have been shown in mostly small studies to be as effective as daily dosing. In general, the same total equivalent weekly dose is given in divided doses over extended dosing intervals.

Most of the published trials evaluating extended dosing intervals have used buprenorphine alone.[33,35-4041] A single trial has investigated the buprenorphine/naloxone combination.[34] Physicians are advised to consult a specialist in opioid dependence treatment before deciding to use extended dosing intervals with buprenorphine/naloxone.

Dosage reduction and treatment discontinuation

The decision to discontinue treatment with buprenorphine or buprenorphine/naloxone should be made as part of a comprehensive treatment plan in partnership with the patient. The best method of discontinuing treatment has not been determined. Patients may be more likely to complete withdrawal using a gradual rather than rapid dosage reduction.[42] Withdrawal symptoms upon abrupt discontinuation or rapid taper of buprenorphine tend to be delayed and milder than with full opioid agonists.

Dosing for medically supervised withdrawal (detoxification)

Studies evaluating sublingual buprenorphine for medically supervised withdrawal have used different sublingual formulations and routes of administration.[43] The bioavailability of the sublingual tablet relative to the solution may vary depending on a number of factors, as described under *Pharmacokinetics*, *Absorption* on page 3. For these reasons, the optimal sublingual tablet dose for detoxification is unclear.

For short-term medically supervised withdrawal, the only available comparative evaluation of optimal buprenorphine dosing suggests that a 5-day course of a high-dose (8 mg/8 mg/8 mg/4 mg/2 mg) regimen may have a slight advantage over a low-dose (2 mg/4 mg/8 mg/4 mg/2 mg) regimen (Grade I). In a fair-quality double-blind, double dummy, randomized pilot trial in 30 inpatients, these two 5-day regimens were compared

with a 5-day regimen of high-dose oral clonidine.[44] The three regimens were shown to be not statistically different in rate of subject completion of the withdrawal regimen and magnitude of blood pressure changes. Both buprenorphine regimens were superior to clonidine in terms of observer-rated withdrawal symptoms. The high-dose, but not the low-dose, buprenorphine regimen was statistically better than clonidine in terms of subject-rated withdrawal symptoms.

Combination buprenorphine / naloxone has also been used for medically supervised withdrawal in a 13-day treatment course. An open-label (fair-quality), randomized effectiveness trial in 113 inpatients and 231 outpatients showed that a 13-day buprenorphine stabilization and withdrawal regimen was superior to 13 days of transdermal clonidine in terms of subject retention and illicit opioid use.[45] Buprenorphine/naloxone was started at 4/1 to 8/2 mg on day 1, 12/3 mg on day 2, 16/4 mg on day 3, and followed by a stepwise reduction to 2/0.5 mg by day 12–13.

Other dosing considerations in medically supervised withdrawal are available in the ***Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction*** **TIP 40** (page 58 of hard copy; page 85/198 in PDF), available at **http://buprenorphine.samhsa.gov/publications.html** .

The optimal dosing strategy for buprenorphine premedication in ultra-rapid, anesthesia-assisted[46] or sedation-assisted[47] opioid detoxification has not been determined, and the risks associated with anesthesia-assisted detoxification may outweigh its benefits, given that safer and similarly effective methods of medically supervised withdrawal are available.[46]

Dosing in special populations

Hepatic disease: Plasma concentrations of buprenorphine and naloxone, which are both extensively metabolized, are expected to be higher in patients with moderate and severe hepatic impairment. Dosage should be adjusted and the patient monitored for symptoms of precipitated withdrawal.

Renal disease: No specific recommendations for dosage adjustment are given. There have been no differences in buprenorphine pharmacokinetics in dialysis and normal individuals. The pharmacokinetics of naloxone in renal failure are unknown.

Elderly: Data are lacking on the use of buprenorphine in individuals 60 years or older. Use caution when dosing buprenorphine in the elderly, particularly during induction.

Patients admitted to hospital: If a patient has been admitted to hospital for reasons other than treatment of opioid dependence, physicians without a waiver may maintain or detoxify the patient with buprenorphine (or methadone) during the hospital stay (21 U.S.C. Section 823 (g)(2) and 21 CFR 1306.07). In this situation, consultation with a qualified physician or addiction specialist should be obtained. If a patient is admitted to hospital primarily for treatment of opioid dependence, then only a DATA-waivered physician can order buprenorphine treatment.

Patients with pain: Patients who require therapy for acute or chronic pain and who are not being treated for addiction should generally be managed within the context of a medical or surgical setting using standard analgesic treatments. Off-label use of

sublingual buprenorphine solely for pain management cannot be supported at the doses available in the U.S. Patients without opioid addiction should not be referred to an opioid maintenance treatment program simply because they have developed physical dependence during opioid therapy.

In patients with pain who are already being treated with buprenorphine for opioid dependence, the once daily administration of sublingual buprenorphine may provide insufficient pain relief. These patients should be treated with a trial of non-opioid analgesics while continuing buprenorphine maintenance. If stronger opioid analgesics are required for either acute or chronic pain, buprenorphine should be discontinued. It should be noted that buprenorphine may block or displace other opioid agonists from receptor sites and can precipitate withdrawal. When buprenorphine is to be restarted, recommended induction doses should be initiated at least 12 hours after the final dose of the opioid analgesic to avoid precipitating withdrawal.

Although it is possible to manage both opioid dependence and pain with buprenorphine—and this option has the advantage of avoiding precipitated withdrawal from the interaction between buprenorphine and opioid agonists—there are no studies that have examined the analgesic effects in buprenorphine-maintained patients, and the optimal dosing regimen of buprenorphine is not known. The dose of sublingual buprenorphine for opioid dependence is generally higher than those used for chronic pain; however, the lower total daily doses of sublingual buprenorphine used for opioid dependence overlap with the upper end of the dosing range evaluated for chronic pain (e.g., 2 to 16 mg per day vs. 0.4 to 3.2 mg per day).[17-20] In the U.S., buprenorphine sublingual tablets in strengths lower than 2 mg are not available and the tablets are not scored.

Efficacy Measures

In trials investigating the use of buprenorphine for substitution (maintenance) treatment of opioid dependence, several efficacy indices have been commonly used as measures of how well substitution therapy met the treatment goal of reducing illicit opioid use. These efficacy variables reflect two of three dimensions of measuring reduction in illicit drug use: (1) retention in treatment reflects the length of time that therapy continues; and (2) urine drug screens reflect reduction in illicit opioid use during therapy. The third dimension, patient outcome after therapy is discontinued under medical supervision, was often not measured in the randomized clinical trials evaluating maintenance therapy.

Clinical Trials

Relative efficacy of buprenorphine for opioid maintenance treatment

The best evidence on the relative efficacy of buprenorphine in comparison with methadone come from meta-analyses of randomized controlled trials (RCTs), including a comprehensive meta-analysis performed by the Cochrane group.[25,48,49] Overall, flexible-dose buprenorphine is slightly inferior to methadone in efficacy.[25,50] However, sublingual buprenorphine is the only agent currently approved for office-based OAT, has a longer duration, causes less pronounced withdrawal effects when discontinued, and can be dosed less frequently in comparison with methadone.

Efficacy is dose-dependent and has been evaluated in studies that used either fixed or flexible dosing schemes. When flexible dosing schemes (which more closely

approximate titration in actual clinical practice) are used, buprenorphine is inferior to methadone in retaining patients on treatment, with a relative risk of 0.82 (95% CI: 0.69 to 0.96).[25] No statistically significant treatment differences were shown for positive urine drug screens (for opioids, cocaine, and benzodiazepines), self-reported heroin use, and criminal activity.[25] Although the treatment difference in terms of discontinuing treatment is relatively small (absolute risk increase, ARI, 0.101), only about 10 patients would need to be treated with buprenorphine to result in one additional patient discontinuing treatment compared with methadone-treated patients (number-needed-to-harm, NNH, 10).[25] It is possible that a faster rate of induction on buprenorphine might improve retention in treatment,[51] but this remains an area that requires further investigation.

With fixed dosing regimens, high-dose buprenorphine (arbitrarily defined as 6 to 12 mg) seems to be better than low-dose methadone (arbitrarily defined as 20 to 35 mg) and less effective than high-dose (arbitrarily defined as 60 to 80 mg) methadone overall.[25] Low-dose buprenorphine (arbitrarily defined as 2 to 4 mg) seems to be similar to low-dose methadone and inferior to high-dose methadone.[25]

Withdrawal symptoms resulting from discontinuation or rapid taper of buprenorphine may be slower to develop and less intense than with full opioid agonists. The role that this characteristic might play, if any, in either facilitating medical discontinuation of treatment or promoting premature discontinuation of buprenorphine (because withdrawal symptoms are less severe than with a full opioid agonist) is unclear.

Limited long-term (up to 3 years) observational studies have shown similar improvements in quality of life and less benzodiazepine use with buprenorphine as compared with methadone.[52]

Buprenorphine Maintenance Therapy in Primary Care Versus Specialized Setting

One study evaluated the impact of treatment setting on the effectiveness of buprenorphine maintenance therapy. In this trial, patients on buprenorphine (up to 32 mg daily) were randomized to either a primary care clinic or an OAT center. Compared with the OAT center patients, primary care patients had numerically but not statistically higher retention in treatment (18/23, 78% vs. 12/23, 52%; p=0.06); a statistically lower rate of illicit opioid use based on overall urine toxicology (63% vs. 85%, p<0.01); and a statistically higher rate of prolonged abstinence (for ≥ 3 consecutive weeks) (43% vs. 13%; p=0.02).[53] The retention rate observed with buprenorphine in primary care seem to be higher than the rates of 40% to 60% usually found in trials comparing buprenorphine with methadone in controlled practice settings.

There have been no studies comparing office-based buprenorphine therapy with either OAT program– or community-based methadone therapy for opioid dependence (DSM-IV).

Response Predictors

Few studies have evaluated whether there are clinical factors which predict a successful outcome with sublingual buprenorphine in primary care treatment of opioid dependence. One study found that treatment outcomes with buprenorphine

provided in a primary care clinic do not vary according to prior methadone treatment.[54] These findings contrasted with those of an earlier meta-analysis which found that patients with prior methadone treatment were more likely to remain abstinent on buprenorphine therapy.[55] In practice, clinicians must consider the level of patient care complexity that they are able to manage before accepting patients for primary care opioid dependence treatment.

There has been no consistency in whether depression or other type of patient characteristics predict a difference in response between the two agents.[56,57,58] Methadone may be more efficacious than buprenorphine as maintenance therapy and reducing cocaine use in patients with concomitant cocaine and opioid dependence[59]; however, additional studies are needed before firm conclusions can be made.

Buprenorphine Maintenance Therapy versus Medically Supervised Withdrawal

In a small but good-quality—and the only long-term (1-year)—placebo-controlled trial identified by the literature search, buprenorphine maintenance therapy was significantly better than a 6-day buprenorphine detoxification regimen followed by placebo in retaining patients in treatment.[60] Five of 20 patients (25%) dropped out (n = 1) or were involuntarily discharged (n = 4) in the buprenorphine maintenance group versus all 20 patients (100%) dropped out in the buprenorphine detoxification/placebo group (p = 0.0001; risk ratio 58.7; 95% CI: 7.4 to 467.4). There was also a significant difference in deaths (none versus 4/20; p = 0.015). There was a significant improvement in addiction severity index (ASI) severity and composite scores over time (including criminality), rare illicit drug use, and high rate of negative urine drug screens (75% of samples) in the maintenance group.

Use of Buprenorphine for Medically Supervised Withdrawal (Detoxification) from Heroin and Other Short-acting Opioids

Several studies have evaluated different methods of detoxification.[61,62] Although the results of a recent trial suggest that anesthesia-assisted rapid detoxification is not recommendable because of an unfavorable risk-to-benefit profile,[46] the optimal opioid agonist or antagonist strategy is unclear.

Buprenorphine is currently the only opioid agonist treatment available for outpatient detoxification. For inpatient detoxification using opioid agonist substitution, either buprenorphine or methadone is available. Providing buprenorphine detoxification therapy in a primary care setting has been shown to be similar in efficacy (retention in treatment) and cost-effectiveness (from the perspective of an Australian health care system) to a specialist clinic.[63]

Short-term trials show that buprenorphine is effective for medically supervised withdrawal[43]; however, evidence of long-term effectiveness of a detoxification-based approach to treatment of opioid dependence—with any agent—is lacking. As mentioned above, buprenorphine maintenance therapy has been shown to be more effective in retaining patients in treatment than medically supervised withdrawal.[60]

Buprenorphine versus clonidine medically supervised withdrawal

In a good-quality meta-analysis, buprenorphine was shown to be associated with less severe withdrawal symptoms and better rates of completion of withdrawal treatment

relative to clonidine (overall RR, 1.38 [95% CI 1.21, 1.57; p = 0.00001]; NNT = 5 [95% CI: 3 to 8).[43] Even very low doses of buprenorphine (1 to 2 mg daily of sublingual tablet or equivalent) seem to be more effective than clonidine in reducing withdrawal symptoms. For better patient comfort and suppression of illicit opioid use, however, higher initial doses are required (6 to 16 mg daily). No definite conclusions can be made when comparing the two drugs in terms of retention in treatment. Buprenorphine may be less likely to be associated with hypotension and hypotension-related treatment discontinuation than clonidine.

A recent randomized field trial showed that therapy with buprenorphine/naloxone sublingual tablets was better than clonidine in a 13-day medically supervised withdrawal regimen[45] and supported the results of the meta-analysis by Gowing, et al.[43]

Buprenorphine- versus methadone-based medically supervised withdrawal

Overall, tapered methadone and buprenorphine seem to be similar in terms of completion of withdrawal and severity of withdrawal symptoms, and no definite differences in risk or type of adverse events have been observed between the two treatments.[43,64]

Combination therapy using buprenorphine plus carbamazepine for medically supervised withdrawal was shown to be better than methadone plus carbamazepine in reducing affective disturbances.[65]

Relative efficacy of buprenorphine-assisted medically supervised withdrawal

In rapid detoxification, the use of buprenorphine (8-mg single dose) as bridge therapy to naltrexone therapy was shown to be similar to an anesthesia-assisted protocol and better than clonidine-based withdrawal in rates of naltrexone induction.[46] The three treatment approaches were otherwise similar in efficacy outcomes (withdrawal symptoms, positive urine drug screens, any drug use, and treatment retention). The buprenorphine-assisted and clonidine-based detoxification interventions were not associated with serious adverse events whereas 3 patients experienced serious adverse events in the anesthesia-assisted detoxification group.

Use of Buprenorphine for Discontinuation of OAT

Limited evidence suggests that patients stabilized on methadone maintenance (30 to 40 mg daily) and tapered to a dose of 30 mg or at which they became "uncomfortable" may be transferred to buprenorphine (4-mg initial dose) then gradually tapered off OAT.[66] Outcome beyond 1 month following discontinuation of OAT was not evaluated.

Another trial showed that a 9-day regimen of buprenorphine (0.15 to 0.9 mg intramuscularly per day) is superior to clonidine (0.3 to 0.9 mg intramuscularly per day) in controlling objective, subjective and psychological withdrawal symptomatology during detoxification from methadone maintenance.[67] It is uncertain whether these results may be applicable to the sublingual and combination formulations of buprenorphine.

Use of Buprenorphine as Interim or Bridge Therapy

Interim therapy with buprenorphine without psychosocial support to reduce patient waiting lists, prior to patient entry into medication assisted rehabilitation programs in Norway, has been shown to be efficacious in terms of treatment retention, self-reported drug abuse, and patient wellbeing.[68] Additional well-designed, U.S. trials are needed to evaluate the efficacy, safety, and feasibility of using buprenorphine in this manner.

Adverse Effects (Safety Data)

Based on their pharmacologic properties, buprenorphine/naloxone and buprenorphine may have four potential safety advantages over other opioid agonist treatments: (1) lower potential for respiratory depression due to overdose (because of a ceiling effect); (2) less physical dependence than methadone (because of its partial agonist properties); (3) lower likelihood of diversion (because of a blockade of euphoric effects from illicit opioid use); and (4) lower likelihood of abuse by injection of the buprenorphine/naloxone tablets (because when injected, naloxone would reverse opioid effects and precipitate withdrawal).

In addition, the withdrawal syndrome produced by discontinuation or tapering of buprenorphine is milder than that seen with full opioid agonists.

The relative and long-term safety of buprenorphine/naloxone and buprenorphine remains to be further evaluated in day-to-day practice settings.

Deaths

A retrospective population-based study performed in France supports the possibility that buprenorphine may be safer than methadone in terms of mortality. The annual rate of overdose deaths from 1994 to 1998 with office-based buprenorphine treatment (6/49,000, 0.0001 to 5/2900, 0.0017) was one third of the rate for methadone (4/5360, 0.0007 to 5/400, 0.0125).[69]

Despite its ceiling effect, buprenorphine tablets, taken orally or sublingually or by injection, has been implicated in fatal drug abuse-related overdoses, particularly when used with benzodiazepines.[70-72,73,74] No correlation between buprenorphine use and deaths was shown in a large multi-database review in the U.K.[73] The same study did show an increase in the number of buprenorphine-related deaths during the first 3 years after 1999, when the high-dose sublingual buprenorphine formulation became available, and therefore the authors recommended continued monitoring.[73]

Buprenorphine diversion and abuse in the U.S.

A manufacturer-sponsored and FDA-mandated postmarketing surveillance of the first 3 years of sublingual buprenorphine/naloxone and buprenorphine monodrug therapy in the U.S. showed few adverse event reports and few or no cases of diversion in seven major metropolitan areas.[75] These findings are reinforced by the findings of a provider network survey that showed a low rate of buprenorphine abuse since marketing of the drug (2002 to first quarter of 2005).[76] Quarterly rates of buprenorphine abuse (< 1 case

per drug abuse expert) were similar to that of tramadol (< 1), a noncontrolled drug, and lower than that for methadone (up to 2) and oxycodone (up to 8).

Other Serious Adverse Events

Overall, in comparative trials, SAEs have been infrequent.

Hepatotoxicity. In a multicenter, double-blind randomized controlled trial comparing four doses of buprenorphine, increased liver enzyme tests of unknown causal relationship to buprenorphine accounted for 14 of 51 (27.4%) serious adverse events reported among 736 patients.[77] Several reports have suggested a possible relationship between buprenorphine and hepatic abnormalities.[78,79,80] Severe hepatitis has also occurred after intravenous misuse of buprenorphine, possibly due to high blood concentrations achieved with parenteral administration of the crushed tablets.[81]

According to the manufacturer, postmarketing data covering the last 5 years showed 103 reports of hepatic adverse events among 60,000 subjects treated per year, equivalent to a rate of about 1 in 3000 cases (written communication, T. Baxter, July 2005). Caution should be exercised when very high doses of buprenorphine (undefined) are used, particularly in patients with preexisting liver (mitochondrial) impairment (e.g., due to alcohol abuse, chronic viral hepatitis, or hepatotoxic drugs such as acetaminophen and isoniazid). Baseline and periodic liver enzymes tests are recommended for buprenorphine-treated patients.[82]

Further surveillance for liver dysfunction is needed to determine if there is an association between buprenorphine and liver dysfunction (also see under *Hepatitis, hepatic events*, page 18**Error! Reference source not found.**).

Tolerability and Adverse Events that Led to Treatment Discontinuation

Tolerability is reflected in treatment retention rates as an efficacy variable (see Table 3 and **Error! Reference source not found.**).

In one study of opioid detoxification, clonidine was associated with lower blood pressure compared with buprenorphine.[83] In another study, 3 (13.6%) of 22 clonidine-treated patients developed hypotension that led to treatment discontinuation (none of the buprenorphine-treated patients discontinued treatment because of hypotension).[84]

Common Adverse Events

Safety data presented in the buprenorphine package insert are available from 3214 opioid-dependent subjects exposed to buprenorphine at doses used in the treatment of opioid dependence.[82]The adverse event profile of buprenorphine is consistent with mild opioid-like effects. Adverse event profiles are similar for buprenorphine/naloxone and buprenorphine at equivalent doses.

In a 4-week trial, the most common adverse events reported with either buprenorphine (N = 103) or buprenorphine/naloxone (N = 107) were headache (29.1% and 36.4%), withdrawal syndrome (18.4% and 25.2%), pain (18.4% and 22.4%), insomnia (21.4% and 14.0%), and nausea (13.6% and 15.0%).[82] These rates were numerically comparable to those observed with placebo (N = 107) except headache (22.4%) and nausea (11.2%) were numerically less common, and withdrawal syndrome (37.4%) numerically more common with placebo.

One comparative RCT found the rate of serious headaches to be higher with buprenorphine than with methadone (33% vs. 23%; p>0.05) and sedation less common with buprenorphine (26% vs. 58%; p=0.014).[51]

Other Adverse Events

Sexual dysfunction. A small, poor-quality, cross-sectional study (N = 54 on methadone or buprenorphine and 51 healthy controls) showed that, relative to methadone, buprenorphine therapy was associated with significantly higher serum testosterone concentrations and lower risk of sexual dysfunction.[85] Well-designed studies are needed to verify these findings.

New adverse events identified postmarketing

In an Indian postmarketing surveillance study, 12 significant adverse events (defined as any effect that was not in keeping with available literature on pharmacologic effects of buprenorphine) were reported, including seizure, epistaxis, dyspnea, fever with chills, constipation, new onset premature ejaculation, improvement in premature ejaculation, anger outbursts, and panic attacks.[10] Increases in liver transaminases (AST and ALT) were reported in 16% to 21% of subjects. The significant adverse events and hepatic events require confirmation and additional monitoring in better designed trials. Generalizability of the findings to the VA and U.S. are limited by a relatively low mean daily dose of buprenorphine (2.9 mg) and differences in culture, demographics, and medical practices.

Hyperlactatemia, which may be severe and associated with potentially fatal lactic acidosis, is a known metabolic adverse effect of antiretroviral nucleoside reverse transcriptase inhibitors. A prospective cross-sectional study of the prevalence and risk of hyperlactatemia (lactate level ≥ 2.25 mmol/l) in HIV-positive patients who were being treated with antiretroviral therapy showed in multivariate analyses that the odds of hyperlactatemia were highest in those treated with buprenorphine (adjusted OR 14.7, 95% CI: 2.55 to 84.35; p = 0.003), followed by combination stavudine-didanosine (OR 3.1; 1.3 to 7.4; p = 0.012) and regimens containing stavudine (OR 2.5; 1.26 to 5.08; p = 0.009), and lowest in older patients (OR 1.04; 1.01 to 1.07; p = 0.01).[86] All of the buprenorphine-treated patients had chronic viral hepatitis C related to injection drug abuse. Further studies are needed to confirm whether buprenorphine is a risk factor for hyperlactatemia in HIV-positive patients and to explore the role of underlying liver disease in the development of high lactate levels. In patients treated with antiretroviral agents (particularly, nucleoside reverse transcriptase inhibitors) and buprenorphine, it would be prudent to check lactate levels intermittently and monitor patients for signs and symptoms of lactic acidosis.

Pregnancy and Lactation

Pregnancy Category: C

The buprenorphine monodrug formulation is preferred over the combination buprenorphine / naloxone formulation for treating pregnant females. Buprenorphine should only be used if the potential benefits outweigh the potential risks to the fetus.

One prospective study reported malformations in 2 of 31 neonates as well as 1 stillbirth and 1 spontaneous abortion among 34 buprenorphine-treated pregnant women.[87]

Neonatal abstinence syndrome of variable intensity has been reported in babies born to mothers exposed to buprenorphine during pregnancy.[87,88,89,90] Prolonged (3 to 9 months duration) motor abnormalities have been noted.[88] One small, preliminary study suggested that hospitalization may be shortened among neonates born to mothers who had been treated with buprenorphine as compared with methadone.[91]

Buprenorphine passes into mother's milk. Therefore, breast feeding is not advised in mothers treated with buprenorphine.

Precautions/Contraindications

Precautions

The precautions for buprenorphine are similar to those of other opioid agonists. Buprenorphine may cause respiratory depression, central nervous system depression, drug abuse, opioid dependence (with prolonged administration), increased intracranial pressure, and orthostatic hypotension. Only the more remarkable precautions are discussed here.

Respiratory depression

Despite having a ceiling effect, buprenorphine has caused respiratory depression, particularly by the intravenous route. Fatalities have occurred when the tablets were misused intravenously or possibly overdosed orally or sublingually, usually with benzodiazepines or other central nervous system depressants.

Naloxone may not be effective in reversing respiratory depression caused by buprenorphine. Ventilation should be supported via mechanical assistance of respiration.

Physical dependence

Chronic administration of buprenorphine produces physical dependence, characterized by withdrawal upon abrupt discontinuation or rapid taper. The withdrawal syndrome is delayed and milder than that seen with full agonists.

Psychological dependence and drug abuse

The use of buprenorphine monodrug tablets for office-based opioid substitution therapy in France led to increased abuse of buprenorphine and the development of a black market for buprenorphine. Melbourne, Australia has also observed a relatively high rate of intravenous abuse of buprenorphine monodrug tablets.[92]

In the U.S., based on its potential for abuse, buprenorphine was reclassified from a Schedule V to a Schedule III drug under the Controlled Substances Act. Its potential for abuse is considered to be less than that of methadone and other Schedule II opioid agonists.

Experts recommend using buprenorphine/naloxone for all phases of treatment, including induction, except if the patient is pregnant or has a documented hypersensitivity to naloxone, then buprenorphine alone is recommended. If buprenorphine monotherapy is to be given for an extended period, precautions should be taken to minimize the possibility

of diversion by experienced opioid addicts and the justification for its use should be documented.

Hepatitis, hepatic events

Animal data suggest that buprenorphine may be directly hepatotoxic.[81] High doses or concentrations, such as may occur in intentional overdoses or intravenous misuse, may increase the risk of liver damage. Cytolytic hepatitis and hepatitis with jaundice have been observed in buprenorphine-treated addicts both in clinical trials and in post-marketing surveillance. Abnormalities have ranged from transient asymptomatic increases in liver transaminases to cases of hepatic failure, hepatic necrosis, hepatorenal syndrome, and hepatic encephalopathy. Many cases involved patients with pre-existing risk factors for liver abnormalities (e.g., hepatitis B or hepatitis C virus, concomitant use of potentially hepatotoxic drugs, and parenteral drug abuse). It is possible that buprenorphine played a causative or contributory role. Liver enzyme tests are recommended at baseline and periodically thereafter. If a hepatic event is suspected, full evaluation to determine its etiology is suggested as well as careful discontinuation of buprenorphine to prevent a withdrawal syndrome and relapse of illicit drug use.

Concomitant use of full opioid agonists

The administration of full opioid agonists shortly before a dose of buprenorphine may result in precipitated withdrawal. Administration of full opioid agonists after a dose of buprenorphine may result in less than the usual analgesic effect of the full agonist. If a clinical situation arises in which administration of a full opioid agonist is indicated (e.g., morphine for acute pain) in a buprenorphine-treated patient, a qualified physician, addiction specialist, and/or pain specialist should be consulted. An adequate interval needs to be allowed between the dose of full agonist and buprenorphine, or buprenorphine withheld until the opioid analgesic is no longer needed. Concomitant treatment with a full agonist should consider the duration of effect of the full agonist relative to that of buprenorphine. If a large dose of full agonist is given to overcome the opioid receptor blockade by buprenorphine, overmedication may result when the effect of buprenorphine dissipates. Reinstitution of buprenorphine should take into consideration the possibility that the use of full agonists in these situations may produce increased opioid tolerance and a higher degree of physical dependence.

QT prolongation and torsade de pointes

High-dose methadone[93] and LAAM[94] have been associated with QT prolongation and torsade de pointes. The potential of buprenorphine to prolong the QT interval has been demonstrated in vitro.[95] There have been no published clinical reports of buprenorphine-related cardiac arrhythmias or QT prolongation. Electrocardiographic monitoring is not recommended at this time.

Contraindications

Hypersensitivity to either drug component

Hypersensitivity to buprenorphine (for both buprenorphine products) or hypersensitivity to naloxone (for buprenorphine/naloxone).

Drug Interactions

CYP 3A4 inhibitors or inducers

If CYP 3A4 inhibitors or inducers are co-administered with buprenorphine, patients should be closely monitored and dosage adjusted if necessary. Increased plasma concentrations of buprenorphine have been observed when it was co-administered with the potent CYP 3A4 inhibitor, ketoconazole. Dose reduction may be indicated if buprenorphine is given with CYP 3A4 inhibitors such as azole antifungal agents (e.g., ketoconazole), macrolide antibiotics (e.g., erythromycin), HIV protease inhibitors (e.g., ritonavir, indinavir, and saquinavir), the antidepressant, nefazodone, or grapefruit juice. The interaction between buprenorphine and CYP 3A4 inducers (e.g., phenobarbital, carbamazepine, phenytoin, and rifampicin) has not been studied.

CNS depressants

Patients who receive buprenorphine with other central nervous system (CNS) depressants (e.g., other opioid analgesics, general anesthetics, benzodiazepines, phenothiazines, other tranquilizers, sedative-hypnotics, or alcohol) may experience increased CNS depression. Consider reducing the dose of one or both agents if the two agents are co-administered. Buprenorphine tablets, taken orally or sublingually or by injection, has been implicated in fatal drug abuse-related overdoses, particularly when used with benzodiazepines.[70-72]

Data Compilation Tables

The manner in which data was presented allowed only limited calculations of clinically meaningful comparisons of treatments (see Table 3). The meta-analysis by Mattick, et al.[25] provided the best data for calculation of relative and absolute risk differences. Based on retention data that showed flexible dosing of buprenorphine to be inferior to flexible dosing of methadone, the calculated relative risk increase was 19%, absolute risk increase, 10%, and number-needed-to-harm (NNH), 10 (95% CI: 6 to 29). The NNH suggests that treatment of just 10 patients with buprenorphine would result in one additional patient dropping out of treatment compared with methadone-treated patients.

Acquisition Costs

Drug acquisition costs

The VA acquisition cost for combination buprenorphine/naloxone is less than that of the buprenorphine monodrug product. (Table 2). The manufacturer preferentially priced the combination product to reduce diversion.

Using estimated equivalent maintenance doses of buprenorphine in combination with naloxone (10 mg daily at a cost of about $4.43 per day) and methadone (50 mg daily at a cost of $0.30 per day), the cost difference for similar outcomes is about $124 per month ($1487 per patient per year) or 15 times greater with buprenorphine plus naloxone. This calculation takes into account drug acquisition costs only.

Extended dosing intervals of buprenorphine would not reduce acquisition costs, as generally the weekly dose would remain the same as for daily dosing.

Table 2 Drug acquisition costs for opioid agonist treatments

	Buprenorphine			Buprenorphine/Naloxone			Methadone			
	2 mg/d	8 mg/d	16 mg/d	2/0.5 mg/d	8/2 mg/d	16/4 mg/d	20 mg/d	80 mg/d	20 mg/d	80 mg/d
	tab	tab	tab	tab	tab	tab	disp tab	disp tab	conc	conc
Cost/Dose	$1.82	$3.42	$6.84	$1.62	$2.81	$5.62	$0.12	$0.48	$0.08	$0.32
Cost/Mo	$54.60	$102.60	$205.20	$49.60	$84.30	$168.60	$3.60	$14.40	$2.40	$9.60

These are lowest available VA prices (effective 28 November 2005). FSS prices for buprenorphine (shown) are available only by **direct purchase**.

Cost Analysis

Published economic analyses applicable to U.S.

The VA Health Economic Research Center performed an economic analysis of buprenorphine. This partial cost-utility analysis, using a hypothetical cohort of injecting drug users, estimated that buprenorphine (based on costs of $5, $15, and $30 per dose) will be less cost-effective than methadone under almost all scenarios in the U.S.[96] The annual costs were $1,825 to $10,950 (plus $3,908 for associated care) with buprenorphine and $5,250 with methadone. The incremental cost per quality-adjusted life-year (QALY) gained for 10% program expansion with no net effect on the number of patients in methadone maintenance for $5, $15, and $30 per dose was $14,000, $26,000, and $44,200, respectively, with a low prevalence of HIV, and $10,800, $20,500, and $35,000, respectively, with a high prevalence of HIV. The findings were sensitive to price per dose.

In comparison, expansion of OAT center capacity has been estimated to have an incremental cost-effectiveness ratio of $8200 to $10,900 per QALY gained. However, expanding OAT centers is less feasible than office-based buprenorphine at this time because of regulatory and other constraints.

Buprenorphine is also a cost-effective treatment in comparison with many other medical treatments provided to opioid-dependent patients, such as trimethroprim-sulfamethoxazole treatment for *Pneumocystis carinii* pneumonia in HIV-infected patients ($16,000 per QALY gained); prophylaxis of *Mycobacterium avium* complex in HIV-infected patients ($35,000 to $74,000); and prophylaxis of cytomegalovirus retinitis ($160,000).[96]

An empirical cost-effectiveness analysis of buprenorphine relative to methadone as currently used in the U.S. or VA has not yet been published. Such studies will need to take into account differences between patients in terms of clinical subgroups,[97] socioeconomic characteristics,[54] and their treatment preferences, as well as the fact that methadone and buprenorphine are not complete therapeutic alternatives for each other.

Conclusions

When a flexible dosing schedule is used, buprenorphine is generally not superior to methadone as substitution treatment of opioid dependence. Response is dose-dependent. Faster induction may improve efficacy, although this possibility needs further evaluation.

The appropriate dosing regimen of buprenorphine in medically supervised withdrawal is unclear. Buprenorphine is more effective and safer relative to clonidine, and similar in effectiveness and safety compared with tapered methadone.

During substitution therapy, buprenorphine may be safer than methadone in terms of lower risk of causing respiratory depression and milder withdrawal symptoms when therapy is discontinued. It may have a lower risk of diversion, psychological dependence, and abuse, although these potential advantages remain to be confirmed in practice-based settings. The effect of the drug on the liver needs further evaluation.

Potentially fatal respiratory depression is possible in spite of the drug's ceiling effect, particularly when the drug is misused intravenously and possibly orally or sublingually. Drug abuse-related fatalities tend to occur in individuals who misused buprenorphine concomitantly with benzodiazepines.

Buprenorphine has been shown to be less cost-effective than methadone maintenance under almost any economic scenario. However, it is a cost-effective health care intervention and is more cost-effective than a number of other medical therapies provided to opioid-dependent patients. Pharmacoeconomic comparisons of buprenorphine and methadone are complicated by the fact that the two agents are not completely therapeutic alternatives for each other.

Compared with methadone, buprenorphine provides the advantages of easier access to treatment, the ability to provide treatment in a less stigmatizing primary care treatment environment (which may enhance treatment efficacy and allow the patient to obtain care for other medical problems), less frequent dosing regimens, less frequent clinic visits, and better safety profile.

Recommendations

Where methadone is accessible in a timely fashion, it should remain the treatment of choice for substitution therapy of opioid dependence. Buprenorphine should be used for maintenance or medically supervised withdrawal in new patients in areas where OAT centers are not available, when the patient does not meet enrolment criteria at an OAT center, when methadone cannot be accessed in a timely fashion, or when restrictive OAT clinic hours would make it difficult for a patient to attend the required daily clinic visits.

Buprenorphine may also be considered for patients who do not obtain the desired clinical outcomes with methadone or who have a documented severe, uncontrollable adverse effect or true hypersensitivity to methadone.

The use of buprenorphine/naloxone and buprenorphine for discontinuation of methadone may be considered on a case-by-case basis.

Sublingual tablets of buprenorphine or buprenorphine/naloxone should not be used for treatment of pain in the absence of DSM-IV criteria of opioid dependence.

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Appendix: Summaries of Clinical Trials

Maintenance Therapy

Citation	Mattick RP, Kimber J, Breen C, Davoli M. Buprenorpine maintenance versus placebo or methadone maintenance for opioid dependence (Review). *The Cochrane Database of Systematic Reviews* 2005;4:4
Study Goals	To provide an evaluation of buprenorphine (BUP) maintenance treatment in the management of opioid dependence.
Methods	• Study Design ➢ Meta-analysis and qualitative review ➢ Databases searched: Cochrane Drugs and Alcohol Review Group Register; Cochrane Controlled Trials Register; 7 electronic databases for published articles without language restrictions, including Medline (1966-2001) and Embase (1980-2001). Numerous other drug and alcohol journals (up to 2001), NIDA monographs, and College on Problems of Drug Dependence Inc. proceedings. References of all identified studies and published reviews. International drug and alcohol treatment conference proceedings were hand searched. Authors of identified RCTs were consulted. ➢ Since most of the RCTs with fixed dosing schedules had more than one dose comparison, treatment groups were broadly classified into "low dose" and "high dose." For methadone (MET), doses between 20 and 35 mg were "low dose" and doses between 60 and 80 mg were "high dose." For BUP, "low dose" included 2 to 4 mg and "high dose" included 6 to 12 mg ➢ Quality assessment: Standardized rating scale based on risk of bias, graded from (A) low, (B) moderate, or (C) high • Data Analysis ➢ A standardized effect size was calculated for each study based on the urine drug screen (UDS) outcome measure reported. ➢ Relative risk (RR) and 95% confidence intervals (CIs) were calculated using a random effect model for retention data (dichotomous outcomes). ➢ A standardized mean difference was calculated for continuous outcomes (UDS, self-reported heroin use, and criminal activity). ➢ Pooled effect size estimate was derived for each domain of measurement. ➢ Test for heterogeneity was used. ➢ Evidence from the meta-analysis and an integrative narrative review were converged
Criteria	• Inclusion criteria ➢ Types of participants: Individuals who were dependent on heroin or other opioids. No distinction was made between those using heroin and those in MET treatment prior to entering the research trial treatment. ➢ Types of intervention: BUP maintenance therapy, using sublingual tablet or ethanol-based solution containing BUP, were compared with MET maintenance therapy or placebo. ➢ Types of outcome measures: Primary outcomes—retention in treatment; urinalysis results positive for heroin metabolite (i.e., morphine); urinalysis results positive for cocaine; urinalysis results positive for benzodiazepines; self report use of heroin; criminal activity. Secondary outcomes—physical health, psychological health, use of other drugs. ➢ Types of studies: All trials of BUP maintenance against MET maintenance or placebo in the management of opioid dependence. Controlled clinical trials which were not randomized may be reviewed qualitatively; only randomized clinical trials were integrated using meta-analysis techniques.

	• **Exclusion criteria** ➢ Studies using MET or BUP for detoxification without a maintenance phase. • **Most recent change:** Study of Mattick 2002 (in press in the previous review) was published as Mattick 2003
Results	• Also see Table 3, page 36. • Of 13 included RCTs (N = 2544), 12 were double-blind, 1 was open-label. Only 2 described methods of allocation concealment and they were adequate. • Most of the patients in the studies included in the analysis were male and about 30 years old, consistent with the general profile of heroin-dependent users. • Flexible-dose BUP vs. flexible-dose MET: MET was more likely to retain patients than BUP (6 studies, 837 participants; RR= 0.82; 95% CI: 0.69 to 0.96). There was no significant difference in positive UDS for morphine (heroin), cocaine, or benzodiazepines. There was also no significant difference in self-reported heroin use (2 studies, 326 patients; SMD –0.10, 95% CI: –0.32 to 0.12) or criminal activity (1 study; SMD = –0.14; 95% CI: –0.41 to 0.14). • Low-dose BUP vs. low-dose MET: No statistically significant treatment difference in terms of retention in treatmen (2 studies, 121 participants)t, and in morphine-positive UDS or cocaine-positive UDS (1 study). Nor was there a significant difference in self-reported heroin use (1 study, 44 patients; SMD –0-.28; 95% CI: –0.35 to 0.90). • Low-dose BUP vs. high-dose MET: Low-dose BUP is not more effective than high-dose MET in retaining patients in treatment (2 studies, 120 participants) nor in suppressing heroin use (morphine-positive UDS; 1 study, 57 participants). However, the overall effect is based on only one study. There was no significant treatment difference in terms of cocaine-positive UDS (1 study, 57 participants). Also, there was no significant treatment difference for self-reported heroin use (1 study, 38 patients). However, results of one study that could not be included in the meta-analysis did show a significant advantage for high-dose MET (65 mg) over low-dose BUP (4 mg). • High-dose BUP vs. low-dose MET: In terms of retention, 1 study favored high-dose BUP, 1 study favored low-dose MET, and 2 studies found no significant difference (positive test for heterogeneity, p = 0.0095). Therefore, no summary measure was provided. In terms of heroin use (morphine-positive UDS), high-dose BUP was superior to low-dose MET (3 studies, 317 participants; SMD = –0.23; 95% CI: –0.45 to 0.01. However, the test for heterogeneity was again positive (p = 0.041), although the direction of the estimates was homogeneous. For cocaine-positive UDS, there was no significant treatment difference (1 study, 59 participants). There was also no significant difference in self-reported heroin use (1 study, 37 patients). • High-dose BUP vs. high-dose MET: There was no significant treatment difference in terms of retention (5 RCTs, 449 participants), but the results (RR = 0.79; 95% CI: 0.62 to 1.01) suggest that high-dose BUP is less likely to retain patients than high-dose MET. High-dose BUP was also inferior to high-dose MET in suppressing heroin use (morphine-positive UDS; 3 studies, 314 participants; SMD = 0.27; 95% CI: 0.05 to 0.50). No significant difference was found for cocaine-positive UDS (1 study, 57 participants) or self-reported heroin use (2 studies, 74 participants). This finding was consistent with the results from one trial that could not be included in the meta-analysis. • Low-dose BUP (2 or 4 mg) vs. placebo, high-dose BUP (8 mg) vs. placebo, and very high-dose BUP (16 mg) vs. placebo were also analyzed but detailed results are not presented here, as this review focuses on active comparators.
Conclusions	Implications for practice: "The implication of the results of the meta-analytic review … are clear for clinical practice. Buprenorphine is an effective treatment for heroin use in a maintenance therapy approach compared with placebo. However, methadone maintenance treatment at high doses is associated with higher rates of retention in treatment and better suppression of heroin use than buprenorphine maintenance treatment. Buprenorphine maintenance should be supported as a maintenance treatment only where higher doses of methadone cannot be administered. The reasons for not applying the best available treatment should be investigated rather than promoting less effective treatment approaches. Given buprenorphine's different pharmacologic properties, it may have advantages in some settings and under some policies where its relative safety and alternate-day administration are useful

	clinically compared to methadone." Implications for research: "There does not appear to be any need for further randomized control trials of the relative efficacy of methadone compared with buprenorphine. There does appear to be a need to undertake studies which will clarify retention in the first few weeks or months of treatment in buprenorphine versus methadone….Problems in the methods of induction onto buprenorphine within the trials analysed might partly explain the inferiority of buprenorphine shown in this review…Other outcome measures such as self-reported drug use, criminal activity, physical health, and psychological health which were too infrequently and irregularly reported in the literature to be analysed in the current review could be included in future studies."
Critique	• Strengths: Literature search was comprehensive and well done. The method for selecting articles was clear, systematic, and appropriate. The quality of the primary studies was evaluated. The results from the studies were combined appropriately. Meta-analysis was performed properly. The results were clinically important. Although the included patients were generally young, there is no definite reason why the results would not be applicable to VA patients. • Limitations: The literature search of the updated systematic review covers publications only up to 2001. Blinded, random selection by the reviewers was not reported. The largest comparative trial of buprenorphine and methadone (N = 405) was published by the same author as the meta-analysis. The evaluators were not blinded to the authors, institutions, or results of the primary studies. No sensitivity analyses were used. Did not take into account differences in bioavailability between buprenorphine tablets and solution. However, conversion of solution doses to tablet doses showed that only one trial had been misclassified under the low-dose instead of high-dose group, and reclassification of that study did not affect the overall results.

Citation	Farre M, Mas A, Torrens M, Moreno V, Cami J. Retention rate and illicit opioid use during methadone maintenance interventions: a meta-analysis. *Drug Alcohol Depend* 2002;65:283-90.
Study Goals	To determine the effect of methadone maintenance strategies on the endpoints of retention rate and reduction of illicit opioid use.
Methods	• Study Design ➢ Meta-analysis of 13 double-blind RCTs; all RCTs had been published since 1972 ➢ PubMed literature search for articles additional reports from review of article reference lists; manual review of tables of contents of journals on drug of abuse included in the psychiatry and substance abuse subject category listing 1997 of the Journal Citation Reports©; the Cochrane Library (1999 issue 4) was used to corroborate completeness of the literature search. ➢ The dose of MET was categorized into two groups: low-dose group (< 50 mg/d) and high-dose group (≥ 50 mg/d). ➢ The dose of BUP was also categorized into low-dose group (< 8 mg/d) and high-dose group (≥ 8 mg/d). • Data Analysis ➢ Logistic regression within a multilevel model framework was chosen for estimation of summary odds ratios (ORs) ➢ Retention in treatment was analyzed as "failure in retention." ➢ Test for homogeneity was used ➢ Model parameters were estimated with M1win using restricted maximum likelihood for final estimates and 95% CIs. ➢ Methadone (MET) at high dose was selected as reference category (OR = 1) for OR calculations.
Criteria	• Inclusion criteria ➢ Double-blind RCTs published in all languages between 1966 and December 1999 ➢ Reference comparators could be placebo, buprenorphine (BUP) or levomethadyl acetate (LAAM). ➢ Length of MET maintenance ≥ 12 wk ➢ Dose of MET clearly stated ➢ Outcome variables: Measures of retention rates in MET treatment and/or illicit opioid use based on analytical determination of drugs of abuse in urine samples • Exclusion criteria ➢ Abstracts of medical meetings
Results	• Also see more detailed results in Table 3 on page 36 and **Error! Reference source not found.** on page **Error! Bookmark not defined.**. • Characteristics of RCTs: Total number of patients—1944 among 13 double-blind RCTs (range: 34 to 430 patients per RCT); mean age—34.4 y; 43% of patients were Caucasian; 64% (n = 1282) received MET, 890 patients were classified in the high-dose group and 392 in the low-dose group; 131 patients received placebo (PBO), 350 BUP (265 received high doses and 85 received low doses), and 181 LAAM. Daily doses—MET 20 to 100 mg; BUP 2 to 12 mg; LAAM 65 or 80 mg 3 times/wk; duration of RCTs—13 to 40 weeks • MET by dose and vs. placebo: Results not reported here (not applicable) • MET vs. BUP: Patients on low-dose BUP showed higher risk of illicit drug use and higher risk of retention failure than those given high-dose MET. No significant treatment differences were found between high-dose MET and high-dose BUP in terms of illicit drug use or retention failure.

Conclusions	Methadone, when administered at doses of 50 mg/d or higher, continues to be the drug of choice for substitution treatment of opioid dependence. BUP and LAAM do not seem superior to MET in terms of efficacy. In the authors' opinions, the most important advantage of BUP and LAAM is the thrice weekly dosing schedule, particularly under policies restricting or forbidding take-home methadone. In addition, BUP and LAAM may be alternatives for some patients who present problems with MET administration or refuse to take the drug. Other benefits related to decreases in HIV risk behavior and criminal behavior, and improvements in health-related quality of life, which have been demonstrated with MET, have yet to be demonstrated for BUP and LAAM.
Critique	• Strengths: Comprehensive literature search; method of selecting articles was clear and systematic; quality of the studies was systematically evaluated using a validated tool (Jadad score); meta-analysis performed properly; results were important. There is no definite reason why the results would not be applicable to VA patients. • Limitations: Selection of articles was not reported to be blinded and in random order; evaluators were not blinded to authors, institutions, and results of the primary studies; sensitivity analyses were not performed; outcome rates and NNT/NNH were not reported.

Citation	Barnett PG, Rodgers JH, Bloch DA. A meta-analysis comparing buprenorphine to methadone for treatment of opiate dependence. *Addiction* 2001;96:683-90. [Performed by the Cooperative Studies Program and Health Economics Resource Center, VA Palo Alto Health Care System]
Study Goals	To present a meta-analysis of five trials that compared buprenorphine with methadone
Methods	• Study Design ➢ Meta-analysis of five RCTs ➢ Medline literature search (prior to 1998), limited to English-language articles • Data Analysis ➢ Urine drug screen (UDS) data of each subject were characterized by a number between zero and one, and the mean of these values was determined for each group. The difference in group means was found for each study. Two different methods were used for missing urinalyses. ➢ For retention data (length of time in treatment), a Cox proportional hazards model was used. The hazard parameter was expressed as the relative risk (RR) of discontinuing buprenorphine treatment compared with methadone. ➢ Differences in the means of the UDS data and differences between the coefficient from the Cox proportional hazards regression were used to determine differences in outcome. ➢ Statistical significance of differences was estimated using variance estimated with the appropriate meta-analysis method. ➢ Homogeneity test was performed.
Criteria	• Inclusion criteria ➢ Peer-reviewed reports of double-blind RCTs that compared methadone with buprenorphine as an opioid substitution therapy published in the English language before 1998 • Exclusion criteria ➢ A sixth trial was excluded because the dose of buprenorphine (2 mg) was too low to be comparable to the data from the other trials.
Results	• Also see more detailed results in Table 3, page 36. • Characteristics of RCTs: Total number of patients—540 among 5 double-blind RCTs (range: 57 to 164 patients per RCT); daily doses—BUP 6 to 12 mg; MET 50 to 80 mg; duration of RCTs—16 to 26 weeks • For UDS results based on 5 RCTs, results were not homogeneous (p = 0.033); therefore, it was not appropriate to report the mean difference in effect. When results were based on 4 RCTs which used ≥ 8 mg of buprenorphine, the homogeneity test was no longer significant and BUP-treated patients had a mean of 8.3% more positive UDSs than MET-treated patients (95% CI: 2.7% to 14%). • BUP-treated patients had 1.26 times the relative risk of discontinuing treatment per unit of time than MET-treated patients (95% CI for difference in risk: 1.01 to 1.57). When the retention analysis was limited to the 4 RCTs that tested 8 mg or more of BUP, the BUP-treated subjects had 1.17 times the risk of discontinuing treatment (p=0.087; 95% CI: 0.93 to 1.48).
Conclusions	The statistically significant differences between BUP and MET do not appear to be of great clinical significance. “The variation between trials may be due to differences in dose levels, patient exclusion criteria and provision of psychosocial treatment. The difference in the effectiveness of buprenorphine and methadone may be statistically significant, but the differences are small compared to the wide variance in outcomes achieved in different methadone treatment programs. Further research is needed to determine if buprenorphine treatment is more effective than methadone in particular settings or in particular subgroups of patients.”

Critique	• Strengths: Meta-analysis was performed properly; results are important; review was performed by VA HERC. There is no definite reason why the results would not be applicable to VA patients. • Limitations: Literature search limited to Medline and English articles; methods for selecting articles were not clear; quality of the RCTs were not systematically evaluated; results were not reported in a clinically meaningful manner (unable to calculate NNTs/NNHs because outcome rates were not provided); patient demographics not reported.

Medically Supervised Withdrawal

Citation	Gowing L, Ali R, White J. Buprenorphine for the management of opioid withdrawal [Systematic Review]. *Cochrane Database of Systematic Reviews* 2005;4:4.
Study Goals	To assess the effectiveness of interventions involving the use of buprenorphine to manage opioid withdrawal, in terms of withdrawal signs and symptoms, completion of withdrawal and adverse effects.
Methods	• Study Design: Systematic review of studies identified from searches of 7 databases (up to October 2003 or September 2004) and reference lists; searches included non-English articles • Data Analysis: Study quality was scored using a standard rating method and the impact of study quality was evaluated by sensitivity analysis. Capacity for quantitative meta-analysis was evaluated; relative risks were calculated for dichotomous data; standardized mean differences (SMDs) were calculated for continuous data; both statistical and clinical heterogeniety were assessed
Criteria	• Inclusion criteria: Randomized and quasi-randomized trials and prospective cohort studies that evaluated buprenorphine for ameliorating signs and symptoms of opioid withdrawal. Studies that provided information on the nature of withdrawal signs and symptoms experienced, the occurrence of adverse effects or rates of completion of the treatment episode. • Exclusion criteria: Studies that investigated combined therapy with buprenorphine and opioid antagonists
Results	• 14 studies (17 reports) on 784 participants (422 treated with buprenorphine) were included out of 70 studies (78 reports) that were reviewed; 11 studies were randomized controlled trials, 1 was partially randomized, and 2 were nonrandomized controlled trials; 10 studies were inpatient, 2 outpatient, 2 were not reported in systematic review • Dosage regimens of buprenorphine were diverse (doses, routes, formulations, treatment duration), making dosage comparisons difficult. When direct dose comparisons were desired, the authors used the manufacturer's estimate of 35% bioavailability of the tablet formulation to convert intramuscular doses to sublingual equivalents. • Interventions among the studies were diverse (adjunctive therapies, withdrawal treatment protocols) and limited the extent of analyses • **Buprenorphine vs. Clonidine (7 studies):** Equivalent sublingual buprenorphine tablet doses were 0.86, 2, and 10.3 mg in 3 studies that used intramuscular administration. Maximum doses ranged from 1.2 to 6 mg/d in 4 studies that used buprenorphine sublingually. Duration of tapering buprenorphine was 3, 4, 5, or 10 days among the 7 studies. Doses were titrated in 1 study (up to 6 mg/d) and fixed in the remaining studies. The combined result for *mean peak withdrawal score* (3 studies) favoured buprenorphine (SMD –0.61, 95% confidence interval –0.86 to –0.36, P < 0.001). The remaining 4 trials generally reported that buprenorphine was better than clonidine using various indicators of relative withdrawal severity. Data on *treatment retention* were presented heterogeneously (3 studies) and could not be meta-analyzed. Analyses of *adverse events* suggested that clonidine may be associated with decreases in blood pressure or discontinuation due to hypotension more often than buprenorphine (4 studies); the remaining studies showed no difference between the two treatments (1 study) or did not report adverse events (2 studies). For completion of withdrawal, the overall relative risk was 1.42 (95% CI 1.22 to 1.66) using urine screening data (1 study) and 1.38 (95% CI 1.21 to 1.57) using completion of schedule treatment data (5 studies) both favoring buprenorphine over clonidine. The latter overall result translates to an **NNT of 5 (95% CI 3 to 8)**, indicating that for every 5 individuals treated with buprenorphine, one additional person can be expected to complete treatment than would be the case with clonidine. • **Buprenorphine vs. Tapering Methadone (3 studies):** Dosage regimens of buprenorphine were 16 mg/70 kg/day i.m. tapered over 12 days; 4 mg/day (unspecified route and formulation) maintained for 3 days then tapered off by day 10; and 3.6 mg i.m. tapered to 1.2 mg over 3 days. Overall, indicators of *withdrawal intensity* generally showed no significant differences between buprenorphine and methadone, although there were isolated time points at which either buprenorphine or methadone was significantly better (2 studies). *Retention in treatment*, measured as average length of

	stay, was 10.8 days for buprenorphine using an average 12-day taper and 12.7 days for methadone using an average 15-day taper (1 study). Either no severe *adverse events* (1 study) were reported or adverse events were not noted (2 studies). Overall, there was no statistically significant difference between buprenorphine and methadone in completion of treatment (RR 1.14, 95% CI 0.87 to 1.50; 2 studies). • **Comparison of different rates of reducing buprenorphine (3 studies):** Dosage regimens were buprenorphine sublingual solution 8 mg/day tapered over 36 vs. 8 days; 8 mg/day (probably sublingual, unspecified formulation) tapered over 2 vs. 8 weeks; and buprenorphine sublingual tablet equivalents of 17 mg/day (in 4 divided doses) for 2 days vs. 8.6 mg/day tapered to 1.6 mg/day on day 5 (given in 2 divided doses). In general, withdrawal signs and symptoms were milder and completion of treatment was more likely when buprenorphine was tapered gradually rather than rapidly; however, data were limited and the results for completion of treatment were contradicted by an excluded trial (the results of which favored faster taper over slower taper). • **Other Comparisons (buprenorphine vs. oxazepam; comparison of different starting doses of buprenorphine):** Buprenorphine dosage regimens were 3 mg/day (unspecified route and formulation) for 7 days then tapered to day 10; and 3, 4.5, or 6 mg sublingually (unspecified formulation) tapered off over 7, 7 or 8 days, respectively. Refer to article for results. • **Managing withdrawal from methadone vs. heroin:** Insufficient data. The use of buprenorphine for withdrawal from methadone seems to be feasible (4 studies included participants withdrawing from methadone). To manage the transition from methadone to buprenorphine, the studies decreased the methadone dose to 30 mg or less and waited at least 24 hours after the last methadone dose before starting buprenorphine.
Conclusions	Buprenorphine is probably more effective than clonidine in decreasing the signs and symptoms of opioid withdrawal and in promoting completion of wihtdrawal treatment. Buprenorphine also appears to be associated with fewer adverse events, particularly symptoms of hypotension and lethargy/tiredness. Buprenorphine appears to be similar in efficacy to methadone for management of opioid withdrawal; however, data are limited. For withdrawal of buprenorphine after a period of maintenance therapy, gradual tapering appears to be preferable to rapid tapering. Additional studies are desirable.
Critique	• Strengths: Used comprehensive souces and search strategies, standard appraise of study quality, test for heterogeneity, and sensitivity testing. Conclusions were consistent with findings. • Limitations: Authors were not consulted; relevant articles published recently (since 2003–2004) were not reviewed.

Table 3 (Part I) Meta-analyses Comparing Buprenorphine and Methadone for Maintenance of Opioid Dependence

			Retention in Treatment	For Discontinuation of Treatment (calculated):			Positive Urine Drug Screens (UDS)			
		Treatment	Results[†]	RRI	ARI	NNH		SMD for Mean Number of Positive UDS, 95% CI (n) for BUP vs. MET		
Reference	N	Daily dose, Duration	Rates, RR, 95% CI (n) for BUP vs. MET	(95% CI)	(95% CI)	(95% CI)	Result(s)	Morphine (M)	Cocaine (C)	BZDP (B)
Mattick (2005)[25] Cochrane meta-analysis of 12 DB and 1 OL RCT published in any language before 2001	2544 in 13 RCTs (51 to 736 pts/RCT)	BUP SL tab or soln, 2 to 32 mg[†] MET 20 to 150 mg Placebo 6 to 52 wk								
		Flexible BUP vs. Flexible MET	BUP < MET (217/411, 52.8% vs. 268/426, 62.9%) RR 0.82 0.69 to 0.96 (837, 6 RCTs)	0.273 (0.057 to 0.253)	0.101 (0.035 to 0.168)	10 (6 to 29)	NSD (for M, C, B)	–0.12 –0.26 to 0.02 (837, 6 RCTs)	0.11 –0.03 to 0.25 (779 pts, 5 RCTs)	0.11 –0.04 to 0.26 (669 pts, 4 RCTs)
		Low BUP (2–4 mg) vs. Low MET (20 to 35 mg)	NSD 0.74 0.52 to 1.06 (121, 2 RCTs)	—	—	—	NSD (for M, C)	NR (1 RCT)	NR (1 RCT)	—
		Low BUP (2–4 mg) vs. High MET (60 to 80 mg)	NSD 0.69 0.45 to 1.06 (120, 2 RCTs)	—	—	—	NSD (for M, C)	0.88 0.33 to 1.42 (57, 1 RCT)	–0.08 –0.60 to 0.44 (57 pts, 1 RCT)	—

	High BUP (6–12 mg) vs. Low MET (20 to 35 mg)	Heterogeneous results (p=0.0095) RR NR (NR, 4 RCTs)	—	—	—	BUP > MET (for M) NSD (for C)	–0.23 –0.45 to –0.01 Test for heterogeneity was significant (p=0.041) but direction of estimates were homogeneous (317; 3 RCTs)	NR (59 pts, 1 RCT)	—
	High BUP (6–12 mg) vs. High MET (60 to 80 mg)	NSD 92/223, 41.3% vs. 117/226, 51.8% 0.79 0.62 to 1.01 (449, 5 RCTs)	—	—	—	BUP < MET (for M) NSD (for C)	0.27 0.05 to 0.50 (314, 3 RCTs)	NR (57 pts, 1 RCT)	—

Table 3 (Part II) Meta-analyses Comparing Buprenorphine and Methadone for Maintenance of Opioid Dependence

			Discontinuation of Treatment	For Discontinuation of Treatment (calculated):			Positive Urine Drug Screens (UDS)	
		Treatment	Results[†]	RRI	ARI	NNH		Difference in Mean % of Positive UDS, 95% CI (n) for BUP vs. MET
Reference	N	Daily dose, Duration	Rates, RR or OR, 95% CI (n) for BUP vs. MET	(95% CI)	(95% CI)	(95% CI)	Result(s)	Illicit Opioids
Farre (2002) [48] Meta-analysis of 13 DB RCTs published in all languages between 1966 and December 1999	1944 (34 to 430/RCT)	Low MET (< 50 mg) High MET (≥ 50 mg) Low BUP (< 8 mg) High BUP (≥ 8 mg) LAAM 65 or 80 mg 3 d/wk	Low BUP < High MET OR 2.72, 1.12 to 6.58 High BUP = High MET OR 1.14, 0.83 to 1.59; p=0.042 (n NR)	ID	ID	For Low BUP vs. High MET: 6 (using a placebo CER of 0.13 (from 2 high-dose MET vs. PBO RCTs)	Low BUP < High MET OR 3.39, 1.87 to 6.16; p=0.0001 High BUP = High MET OR 1.08, 0.75 to 1.57; p=0.68	—
Barnett (2001)[50] Meta-analysis of 5 DB RCTs published in English before 1998	540 in 5 RCTs (57 to 164/RCT)	BUP 6 to 12 mg MET 50 to 80 mg 16 to 26 wk	BUP < MET Rates NR RR 1.26, 1.01 to 1.57 (p=0.019) (540, 5 RCTs)	0.263	ID	ID	Heterogeneous results (p=0.034) with 5 RCTs BUP < MET when 1 RCT (that used BUP 6 mg) was excluded	NR 0.083 0.027 to 0.140 (p=0.002) (478, 4 RCTs using BUP 8 mg)
		BUP 8 to 12 mg Low-dose MET 20 to 30 mg	NSD Rates NR RR 0.86, 0.66 to 1.22 (314, 3 RCTs)	—	—	—	BUP > MET	–0.084 –0.012 to –0.156 (314, 3 RCTs)

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Footnote to Table 3:

B or BZDP = Benzodiazepine; BUP = Buprenorphine; C = Cocaine; MET = Methadone; M = Morphine (heroin metabolite); NNH = Number-needed-to-harm; the number of patients who, if they received buprenorphine, would lead to one additional patient being harmed (i.e., discontinuing treatment) compared with patients who received control treatment (i.e., methadone); PBO = Placebo; SMD = Standardized mean difference

> means superior to

NSD means *no statistically significant difference* between treatments

† This meta-analysis did not take into account differences in bioavailability between sublingual tablets and solution. The bioavailability of tablets is estimated to be 50% to 70% greater than that of the solution. When doses for buprenorphine solution are converted to an estimated equivalent dose of tablets using a bioavailability of 50% (to be conservative), one study (Schottenfeld 1997) in the meta-analysis could be reclassified from low-dose to high-dose buprenorphine. The treatment differences between buprenorphine and methadone at low and high doses after adjustment were still not statistically significant.