National PBM Drug Monograph

Buprenorphine and Buprenorphine/Naloxone (SUBUTEX and SUBOXONE)

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

Executive Summary

- Buprenorphine and buprenorpine/naloxone are the first agents to become available in the U.S. for office-based treatment of opioid dependence under the Drug Abuse 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 and buprenorphine/naloxone are generally not superior to methadone or LAAM as maintenance of opioid dependence but they are more expensive. Drug acquisition costs are 29 times higher and cost-effectiveness lower than that for methadone under almost all economic scenarios.
- Buprenorphine and buprenorphine/naloxone 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.

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. For instance, many patients do not seek treatment because of the stigma associated with methadone treatment or are unable to comply with the required daily visits for methadone treatment.

According to a study performed in 1999 by the Health Economics Research Center, Center for Health Care Evaluation, VA Health Care System, there were about 30,000 veterans treated for opioid dependence and this number probably represented less than 20% of all veterans with opioid dependence (verbal communication, J. Trafton, 12 December 2002). A Drug and Alcohol Program Survey (DAPS) in 2000 found that

there were 663 opioid-dependent veterans waiting to be treated at 246 VA substance abuse treatment centers, of which 33 were OAT centers. There are currently about 4700 veterans being treated among 37 OAT centers. Although four new centers have been started in the past two 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 are launched in early January 2003, they will be the first agents available in the U.S. for office-based treatment of opioid dependence under the Drug Abuse 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 eliminates 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. represents a paradigm shift in the treatment of opioid dependence. It is the first major viable attempt to increase the accessibility, convenience, and acceptability of OAT since the introduction of methadone clinics.

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 the mu-opioid receptor than full agonist opioids and may block or displace other opioid agonists from receptor sites.

While 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 precitated withdrawal syndrome is difficult to reverse because of the high affinity of buprenorphine for the opioid receptor.

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.

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 been estimated to be 40% to 50% of the solution in one study[3] and 75% to 80% in another study.[4] There may be considerable inter-individual variability in bioavailability of the tablet relative to the solution.[5] The difference in bioavailability between the tablets and solution needs to be taken into account when evaluating studies.

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.

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

Off-label Uses

Pain management. Sublingual buprenorphine in doses much smaller than those used for opioid maintenance therapy has been shown in double-blind randomized controlled trials (RCTs) to be effective for acute post-operative pain.[6-10] Sublingual buprenorphine has also been demonstrated to relieve chronic pain to a degree not statistically different from phenytoin in one small double-blind RCT[11] and less effectively than tramadol (100 mg

orally every 8 to 12 hours) in a randomized trial [blinding not stated][12]). 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).[6-10] 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).[11-14] 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 generally first be tried on standard analgesic treatments.

Current VA National Formulary Status

Non-formulary with criteria for use

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 alone is recommended for induction and the buprenorphine/naloxone combination is recommended for maintenance or when clinical use includes unsupervised administration. Unsupervised administration of buprenorphine alone should be limited to patients who cannot tolerate naloxone (e.g., patients with a documented hypersensitivity to naloxone).

Buprenorphine 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.

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 *Buprenorphine Curriculum for Physicians* and *Buprenorphine Clinical Practice Guidelines* available from the Center for Substance Abuse Treatment (CSAT) (see http://buprenorphine.samhsa.gov/bwns/Curriculum.html).

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

Induction

For induction, the use of buprenorphine alone is recommended over the buprenorphine/naloxone combination product, although there have been no studies comparing the two products for induction and there is no contraindication to using the combination product for induction. It is important to start induction with buprenorphine 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 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. Therefore, to avoid precipitating withdrawal symptoms when conversion from methadone or other long-acting opioid to buprenorphine, it is recommended 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. The induction dose of buprenorphine should start at a minimum of 2 mg, repeating doses as needed up to 8 mg in 24 hours.

There are no studies evaluating induction with buprenorphine in LAAM-treated patients. The CSAT document *Buprenorphine Clinical Practice Guidelines* (available at: http://buprenorphine.samhsa.gov) recommends that the dose of LAAM be tapered down to 40 mg or less every other day and buprenorphine should be started at least 48 hours after the last dose of LAAM. 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. The buprenorphine/naloxone combination should be started on day 3 at the same dose as day 2 (e.g., 12 mg/3 mg if 12 mg buprenorphine was given on day 2) then titrated to achieve an adequate maintenance dose.

Using the buprenorphine/naloxone combination product, 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.[15]

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 buprenorpine is possible due to the drug's long duration of action.

Alternate-day dosing,[16-20] thrice weekly,[21-23] every-third-day,[20,23] and every-fourth-day[23] dosing of buprenorphine have been studied. 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.[16-23] A single trial has investigated the buprenorphine/naloxone combination.[17] 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. There have been no controlled trials comparing different methods of tapering doses; therefore, the best method of discontinuing treatment has not been determined. Both gradual and abrupt discontinuation of drug have been used, but gradual dosage reduction in stable patients is preferred. Withdrawal symptoms upon abrupt discontinuation or rapid taper of buprenorphine tend to be delayed and milder than with full opioid agonists.

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.

Patients admitted to hospital: Under DATA 2000, physicians without a waiver are allowed to *continue* buprenorphine treatment in patients who are already receiving buprenorphine and are admitted to a hospital (such physicians are not allowed to *start*

buprenorphine treatment). When a patient on buprenorphine is admitted to a hospital, consultation with a qualified physician or addiction specialist should be obtained.

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 buprenorphone maintenance. If stronger opioid analgesics are required for either acute or chronic pain, then 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).[11-14] In the U.S., buprenorphine sublingual tablets in strengths lower than 2 mg are not available and the tablets are not scored.

Adverse Effects (Safety Data)

Based on their pharmacologic properties, buprenorphine and buprenorphine/naloxone 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 and buprenorphine/naloxone 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-base 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).[24]

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.[25-27]

Other Serious Adverse Events

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.[28]

Further surveillance for liver dysfunction is needed to determine if there is an association between buprenorphine and liver dysfunction (also see under Precautions/Contraindications). (N.B.: The FDA has requested Reckitt Benckiser to submit a protocol for a prospective study designed to determine the effect of buprenorphine on the liver compared with a methadone-treated control group.)Overall, in comparative trials, SAEs have been infrequent.

Tolerability and Adverse Events that Led to Treatment Discontinuation

Tolerability is reflected in treatment retention rates as an efficacy variable (see Table 3 and Table 4).

In one study of opioid detoxification, clonidine was associated with lower blood pressure compared with buprenorphine.[29] 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).[30]

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.[15] The adverse event profile of buprenorphine is consistent with mild opioid-like effects. Adverse event profiles are similar for buprenorphine and buprenorphine/naloxone 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%).[15] 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).[31]

Pregnancy and Lactation

Pregnancy Category: C

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

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 tablets for office-based opioid substitution therapy in France led to increased abuse of buprenorphine and the development of a black market for buprenorphine. 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.

Naloxone was added to discourage the intravenous misuse of buprenorphine. 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.

Buprenorphine alone is recommended for induction and its use should be limited to short periods (e.g., the first 2 days of induction). Buprenorphine/naloxone is recommended for the remainder of treatment unless the patient has a documented hypersensitivity to naloxone. In cases such as this, 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

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[32] and LAAM[33] have been associated with QT prolongation and torsade de pointes. The potential of buprenorphine to prolong the QT interval has been demonstrated in vitro.[34] 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 antifunal 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.[25-27]

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 or LAAM come from meta-analyses of randomized controlled trials (RCTs), including a recent, comprehensive meta-analysis performed by the Cochrane group.[35-38] Overall, the efficacy of buprenorphine is comparable to that of methadone, with rates of retention in treatment and percentage of negative urine drug screens around 40% to 60% or lower.[35,39] (There is also a substantial placebo effect with rates of retention around 40% to 45%.[35])

- 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 and no different from methadone in terms of positive urine drug screens. 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).[35] It is possible that a faster rate of induction on buprenorphine might improve retention in treatment,[31] but this area requires further investigation.
- With fixed dosing regimens, buprenorphine 6 to 12 mg may be superior to methadone 20 to 35 mg in terms of suppressing heroin use; however, study results have been inconsistent.[35] Buprenorphine 6 to 12 mg is inferior to methadone 60 to 80 mg in suppressing heroin use.[35] The clinical applicability of this treatment difference may be limited because methadone is often prescribed at lower doses (more than 50% of VA patients on stable opioid agonist doses receive less than the minimum recommended methadone dose of 60 mg[40]). Limited studies have not found a statistically significant difference between lower doses of buprenorphine (2 to 4 mg) and low (20 to 35 mg) or higher (60 to 80 mg) doses of methadone in terms of retention on treatment or suppressing heroin use; however, the sample sizes were small.[35]
- By extrapolation of results from the meta-analysis by Mattick, et al.,[35] 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).
- Providing buprenorphine in a primary care setting as compared with a traditional OAT center may also improve rates of efficacy. In one RCT, 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).[41] 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.
- 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.[42-44] No published studies comparing medical maintenance with office-based buprenorphine were found.
- Additional RCTs are needed to compare higher doses of methadone (greater than 80 mg daily) with buprenorphine.

- 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.
- Less than daily dosing regimens are possible with buprenorphine because of its long duration of action. Although patients may experience more withdrawal symptoms with extending dosing intervals, they may prefer less frequent doses over daily doses.[16,23] Alternate-day dosing[16-20] thrice weekly[21-23] every-third-day,[20,23] and every-fourth-day[23] dosing have been shown to be similar in efficacy to daily dosing of buprenorphine; however, most studies were small, used buprenorphine alone, and have focused attention on alternate-day and thrice weekly dosing. One trial involved the buprenorphine/naloxone combination.[17] Thrice weekly dosing of buprenorphine (16 to 32 mg) has been shown to be superior to low-dose methadone (20 mg daily) and not statistically different from high-dose methadone (60 mg daily or greater) and levomethadyl acetate (75 to 115 mg thrice weekly).[37] Administration every fifth day is less effective than daily and every-third-day dosing.[45]

Use of Buprenorphine for Detoxification from Heroin and Other Short-acting Opioids

- There are no published studies of rapid (≤ 3-day) opioid detoxification using the buprenorphine or buprenorphine/naloxone sublingual tablets. When compared with clonidine for rapid opioid withdrawal in a small (N = 25), double-blind randomized controlled trial, the parenteral form of buprenorphine (administered intravenously or sublingually) was more effective in relieving early withdrawal symptoms and was better accepted by patients.[29] In addition, clonidine was associated with lower blood pressure. Because the dropout rate was higher with clonidine (5 of 13, 38.5%) than with buprenorphine (2 of 12, 16.7%), the study is subject to attrition bias. Long-term outcomes from rapid opioid withdrawal using buprenorphine have not been reported; however, studies using other detoxification treatments have found that short withdrawal periods result in minimal long-term benefits.[46]
- Insufficient number of studies, variability among studies, and low-quality study design prohibit conclusions about appropriate treatment regimens and potential benefits and risks from the use of buprenorphine in the short- and moderate-period (< 28-day) management of opioid withdrawal symptoms.[47]

Use of Buprenorphine for Discontinuation of OAT

- Limited evidence suggests that a 9-day regimen of buprenorphine (0.15 to 0.9 mg per day) is superior to clonidine (0.3 to 0.9 mg per day) in controlling objective, subjective and psychological withdrawal symptomatology during detoxification from methadone maintenance.[48]

Summaries of Clinical Trials (Maintenance Therapy Only)

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* 2002:4.
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; 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 • 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.
Results	• Also see Table 3, page 26. • Of 13 included RCTs, 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. 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). • Low-dose BUP vs. low-dose MET: No statistically significant treatment difference in terms of retention in treatment, morphine-positive UDS, or cocaine-positive UDS. 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 nor in suppressing heroin use (morphine-positive UDS). However, the overall effect is based on only one study. There was no significant treatment difference in terms of cocaine-positive UDS. Also, there was no significant treatment difference for self-reported heroin use (1 study, 38 patients; SMD –0.06; 95% CI: –0.70 to 0.58). 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. 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. There was also no significant difference in self-reported heroin use (1 study, 37 patients; SMD –0.64; 95% CI: –0.06 to 1.33). • High-dose BUP vs. high-dose MET: There was no significant treatment difference in terms of retention, 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). No significant difference was found for cocaine-positive UDS or self-reported heroin use (2 studies, 74 patients; SMD –0.02; 95% CI: –0.48 to 0.45). 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: Blinded, random selection by the reviewers was not reported. The largest comparative trial of buprenorphine and methadone (N = 405) was in preparation for submission for publication 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 26 and Table 4 on page 29. • 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 26. • 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 $\geq$ 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.

Citation	West SL, O'Neal KK, Graham CW. A meta-analysis comparing the effectiveness of buprenorphine and methadone. *J Subst Abuse* 2000;12:405-14. [Article was not available for review at the time of report preparation. Summary of study was taken from the study abstract.]
Study Goals	To provide a meta-analysis of all available research reporting a controlled comparison of buprenorphine and methadone.
Methods	• Study Design ➢ Meta-analysis • Data Analysis ➢ Not reported
Criteria	• **Inclusion criteria** ➢ Not reported • **Exclusion criteria** ➢ Not reported
Results	• Not reported
Conclusions	Findings suggest a relative equality in the efficacy of buprenorphine and methadone, although patients receiving methadone were less likely to test positive for illicit opiate use. Past experience with methadone maintenance acted as a moderating variable, however, such that those receiving buprenorphine were more likely to stay drug-free in studies that included patients with prior methadone experience.
Critique	• Strengths: Unable to assess • Limitations: Information obtained from abstract of study report.

Acquisition Costs

Drug acquisition costs

The VA acquisition cost for buprenorphine with naloxone is $2.93 for the 8-mg tablet and more than one half of that for the 2-mg tablet (Table 2). VA prices for buprenorphine without naloxone were not available.

Using estimated equivalent maintenance doses of buprenorphine in combination with naloxone (10 mg daily at a cost of about $4.60 per day) and methadone (50 mg daily at a cost of $0.20 per day), the cost difference for similar outcomes is about $132 per month ($1584 per patient per year) or 23 times greater with buprenorphine plus naloxone.

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/Naloxone (mg/d)			Methadone (mg/d)				LAAM (mg 3x/wk)	
	2	8	16	20	80	20	80	20	80
Cost per:	tab			disp tab		conc		soln	
Dose	$1.66	$2.93	$5.86	$0.08	$0.33	$0.06	$0.26	$0.29	$1.18
Month	$49.65	$87.84	$175.68	$2.46	$9.84	$1.96	$7.84	$3.48	$14.16

Prices reflect lowest VA-State Veterans Base prices for buprenorphine and lowest Federal Supply Schedule prices for methadone and LAAM as of 27 May 2003. Prices for buprenorphine without naloxone were not available.

Cost Analysis

Published economic analyses

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.[49] 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).[49]

Data Compilation Tables

The manner in which data was presented allowed only limited calculations of clinically meaningful comparisons of treatments (see Table 3 and Table 4). The meta-analysis by Mattick, et al.[35] 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 27%, 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.

Conclusions

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

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.

The appropriate dosing regimen and risks and benefits of buprenorphine in medically supervised detoxification relative to clonidine are unclear. However, buprenorphine appears to be safer than clonidine in terms of potential to cause hypotension.

Buprenorphine is 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.

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 new patients in areas where OAT centers are not available, when the patient does not meet enrolment criteria at an OAT center, when methadone or LAAM 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.

Patients who are stable on methadone or LAAM maintenance should continue with methadone or LAAM.

If a patient has difficulty making the required clinic visits for methadone therapy, LAAM (which can be dosed thrice weekly) should be considered before buprenorphine.

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 or LAAM.

Recommendations for criteria for use of buprenorphine in medically supervised detoxification cannot be made at this time. The use of buprenorphine and buprenorphine/naloxone for discontinuation of methadone or LAAM maintenance therapy may be considered on a case-by-case basis in patients who do not tolerate a tapered dosage reduction of either drug or the use of alpha$_2$-adrenergic agonists (e.g., clonidine) for blocking withdrawal symptoms.

Sublingual tablets of buprenorphine or buprenorphine/naloxone should not be used for treatment of pain.

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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 2002[35] 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 [36] 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)[39] 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)

cont'd

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.

Table 4 Efficacy Comparisons Between Buprenorphine and Levomethadyl acetate (LAAM)

			Retention in Treatment	For Discontinuation of Treatment (calculated):			Positive Urine Drug Screens (UDS)
		Treatment	Results†	RRI	ARI	NNH	
Reference	N	Daily dose, Duration	Rates, RR, 95% CI (n) for BUP vs. LAAM	(95% CI)	(95% CI)	(95% CI)	Result(s)
Johnson (2000)[37] R DB DD SC Age: 36–37 y Sex: 60% to 73% male Jadad score: Good (3)	220	BUP 16 to 32 mg (flexible) LAAM 75 to 115 mg (flexible) MET 60 to 100 mg (flexible) MET 20 mg (fixed) x 17 wk	BUP = LAAM BUP, LAAM, or MET60–100 > MET20 (p<0.001) Calc. RR (BUP vs. LAAM) 1.09 58%, 53%, 73% vs. 20% (N=55 per group)	—	—	—	% of UDS positive for opioids per week: BUP ~ LAAM, and BUP, LAAM, or MET60–100 > MET20, (mean ± SE, 95% CI) 62 ± 4, 55 to 70 vs. 52 ± 4, 44 to 60 (p=0.005; N=55 per group) ≥ 12 consecutive UDS negative for opioids: BUP, LAAM, or MET60–100 > MET20 (26%, 36%, 28% vs. 8%; p<0.005) ≥ 12 consecutive UDS negative for cocaine: BUP, LAAM, or MET60–100 > MET20 (30%, 36%, 38% vs. 14%; p=0.02)