Review

Buprenorphine: how to use it right

Rolley E. Johnson a,1,* , Eric C. Strain a, Leslie Amass b

a Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, 5510 Nathan Shock Drive, Baltimore, MD 21224, USA
b Friends Research Institute, Inc., Los Angeles, CA 90025, USA

Received 19 December 2002; accepted 4 February 2003

Abstract

The unique pharmacology of buprenorphine at the mu-opioid receptor (i.e. high affinity, low intrinsic activity and slow dissociation) results in buprenorphine having: (1) a good safety profile, (2) low physical dependence, and (3) flexibility in dose scheduling. Early studies assessed the effectiveness of buprenorphine for the treatment of opioid dependence using a sublingual solution formulation. More recently, a combination tablet (buprenorphine/naloxone in a 4:1 ratio) has been assessed with the goal of decreasing diversion and abuse. Controlled studies with buprenorphine solution, buprenorphine mono-tablet, and buprenorphine/naloxone combination tablet have uniformly demonstrated the effectiveness of buprenorphine for opioid dependence treatment and the combination tablet appears to decrease (but not eliminate) abuse potential. There is general agreement across studies regarding buprenorphine induction and maintenance dose schedules. The clinical effects of buprenorphine and buprenorphine/naloxone are similar and most patients can be treated initially with and maintained on a daily buprenorphine/naloxone dose of 4:1/24:6 mg. Dosing is possible on a less-than-daily schedule; however, multiples of the daily-dose should be administered to cover the increased interval between doses. If buprenorphine withdrawal is indicated, gradual dose reduction is recommended over a rapid dose reduction or abrupt cessation. Both tablet formulations are approved by the US FDA for opioid dependence treatment as Schedule III narcotics and are, therefore, available for use in office-based practice. The buprenorphine plus naloxone combination product should provide additional safeguards for use in office-based practice by decreasing risk of diversion, and office-based treatment should expand the availability of services to opioid dependent patients.

Keywords: Buprenorphine; Buprenorphine/naloxone; Induction; Maintenance; Dose reduction; Opioid dependence; Treatment

1. Introduction

It is estimated there are at least 898 000 chronic users of illicit opioids in the US (Office of National Drug Control Policy, 2002). For the past several decades, there have been only two types of medications approved for the treatment of opioid dependence in the US (although in some European countries the alpha-adrenergic agonist lofexidine is approved for medical withdrawal from opioids). The first type of approved medication, agonist substitution therapies, consists of methadone and LAAM. It is estimated that 179 000 patients receive this type of treatment in the US (American Methadone Treatment Association, 1999). These medications produce morphine-like agonist effects and cross substitute for heroin. Both have proven to be extremely effective in reducing illicit opioid use and maintaining patients in treatment. However, some people view these medications as less than adequate treatments since they “merely substitute one addiction for another.” The second type of medication for the treatment of opioid dependence is antagonist therapy, and the one medication approved for this use is naltrexone. Unlike agonist therapies, naltrexone does not produce morphine-like subjective effects. Naltrex-
one, a full opioid antagonist, is an excellent medication pharmacologically (i.e. it blocks the effects normally observed following the administration of an opioid); however, it is difficult to retain patients in treatment due to a lack of desired positive subjective effects. While rates of naltrexone use for the treatment of opioid dependence are not known, general clinical impression is that antagonist therapy is used relatively infrequently compared with agonist therapy.

The pharmacology and clinical use of these therapies is straightforward given that these medications are either full agonists or antagonists. In general, the dose of methadone or LAAM is increased until opioid craving, illicit opioid use, and withdrawal symptoms have abated or until excessive side-effects (i.e. sedation, constipation, etc.) require a reduction in dose. Likewise, naltrexone is used on a daily or thrice-weekly schedule to produce blockade of illicit opioids.

With the discovery of multiple opioid receptors, newer opioid analgesics (mixed agonist/antagonists and partial agonists) have been developed to take advantage of the pharmacologic effects mediated by these receptors. This development effort has been aimed primarily at reducing the abuse potential and physical dependence properties of these medications, while maintaining analgesic efficacy. These medications have varying degrees of affinity and intrinsic activity at different opioid receptors, and thereby can produce a more complex array of pharmacological effects than observed with full agonists or antagonists. The array of pharmacologic effects elicited by these medications has clinical implications. In the case of buprenorphine, it has high affinity and low intrinsic activity at the mu receptor (i.e. partial agonist). Buprenorphine has high affinity for and produces antagonist properties at the kappa receptor. This unique pharmacologic profile at the mu and kappa receptors gives buprenorphine certain advantages over the other mixed agonist–antagonist medications as it relates to the treatment of opioid dependence. These advantages include a greater safety index relative to respiratory depression, less autonomic signs of opioid withdrawal, and less psychomimetic or dysphoric effects.

Although labeled as a mixed agonist/antagonist for its activity at the mu and kappa receptors, respectively, it is the partial agonist properties buprenorphine exhibits at the mu receptor that are thought to be primarily responsible for its effectiveness in treating opioid dependence. Under appropriate conditions, buprenorphine may interact with opioid receptors to act as an agonist (morphine-like) or as an antagonist (naloxone-like). As such, buprenorphine combines several of the strengths of methadone, naltrexone, and LAAM (cf. Bickel and Amass, 1995). Like methadone and LAAM, buprenorphine is an opioid agonist that is reinforcing (and hence can maintain compliance with regular ingestion). Like methadone, naltrexone and LAAM, it blocks the effects of illicit opioids, and like naltrexone and LAAM, it can be dosed on a less-than-daily basis. Like naltrexone, under the appropriate conditions buprenorphine can cause a withdrawal syndrome when administered to a person dependent on opioids.

Thus, buprenorphine can be visualized on a continuum between a full agonist (i.e. morphine, methadone, and LAAM) and an antagonist (i.e. naloxone, nalmefene and naltrexone) (Fig. 1). In individuals not tolerant to opioids, it acts as a potent mu-opioid (i.e. morphine-like) agonist at low doses. However, as the dose of buprenorphine is increased, it produces maximal agonist effects that are less than that expected from a full mu-opioid agonist. Further, as a result of its partial agonist properties, a high dose of buprenorphine may cause opioid-like withdrawal signs and symptoms (i.e. appearing to function as an opioid antagonist) in persons who have a high level of physical dependence on other opioids.

However, like methadone and LAAM (but unlike naltrexone), buprenorphine also has the disadvantage that it can be abused (Pickworth et al., 1993; Strain et al., 1997; Comer et al., 2002a; Comer and Collins, 2002b). Because this liability could significantly impact the ultimate role of buprenorphine in the treatment of opioid dependence (Agar et al., 2001), a combination product of buprenorphine and naloxone (Suboxone®) was developed. By reducing the abuse liability of buprenorphine, it can be made acceptable for use by clinicians outside of opioid treatment programs (i.e. office-based treatment setting). If buprenorphine were available through the traditional opioid treatment program system, it is likely that additional numbers of new patients entering the treatment delivery system would be limited (as appeared to be the initial case with LAAM). The US Food and Drug Administration approved buprenorphine and buprenorphine/naloxone on 8 October 2002 for the treatment of opioid dependence. Therefore, it is available in new treatment delivery sites such as office-based practices and this should result in an increase in the number of patients accessing treatment.

Office-based care will be possible due to a change in legislation driving the delivery of narcotic addiction treatment (Jaffe and O’Keeffe, 2003). Congress passed the Children’s Health Act of 2000 (P.L. 106-310) on 17 October 2000. Title XXXV of this law provides a “Waiver Authority for Physicians Who Dispense or Prescribe Certain Narcotic Drugs for Maintenance Treatment or Detoxification Treatment” of opioid-dependent individuals. This part of the law is known as the Drug Addiction Treatment Act (2000) (Bowerwright, 2002). Under this law physicians can treat opioid-dependent patients from their office with FDA approved schedule III, IV and V narcotics by notifying
Fig. 1. Comparison of the dose-related effects of buprenorphine and methadone. Buprenorphine may appear to have either opioid “agonist-like” or “antagonist-like” properties. In individuals not tolerant to opioids, it acts as a potent mu-opioid (i.e. morphine-like) agonist at low doses (light shading). Maximal agonist effects, equivalent to approximately 60–100 mg of oral methadone occurs at a sublingual dose of about 24 mg (dark shading). As the dose of buprenorphine is increased, its effects are less than those expected from a full mu-opioid agonist. Duration of effect is also increased as the dose is increased. However, in opioid-dependent individuals, high doses of buprenorphine may acutely precipitate an opioid withdrawal syndrome (secondary to buprenorphine’s partial-agonist character), making buprenorphine appear to function as an opioid antagonist (e.g. naltrexone).

Fig. 2. Hypothetical dose–effect curve for buprenorphine. As the dose increases (X-axis) the effect increases (Y-axis) to a maximum (M) and then the effect decreases as the dose is further increased.
seen when an antagonist such as naloxone or naltrexone is administered (as described in more detail below).

While under certain circumstances buprenorphine can clinically appear to function as a mu opioid antagonist (due to its partial agonist properties), this occurs rarely. More commonly, the effects of buprenorphine are those associated with other opioid agonists such as morphine and methadone. For example, in experienced opioid abusers, acute doses of buprenorphine are identified as an opioid agonist (Jasinski et al., 1978; Johnson et al., 1989; Pickworth et al., 1993; Schuh et al., 1999; Amass et al., 2000c; Strain et al., 2000; Comer et al., 2002a). However, while buprenorphine demonstrates morphine-like agonist effects at low doses, there is only a minimal increase in agonist effects at higher doses (i.e. mu agonist effects on both subjective and physiologic measures plateau at high doses) (Walsh et al., 1995b). Thus, for acute doses, the maximal euphoria and opioid-like scores obtained with buprenorphine appear to be in the range of 60 mg oral methadone, which would be equivalent to approximately 30 mg parenteral morphine, or 15 mg parenterally heroin.

### 2.2. Absorption/distribution/metabolism/elimination

Early studies with buprenorphine used a sublingual, alcohol-based solution. In non-dependent and dependent opioid abusers, approximately 50% of a sublingually administered dose of this buprenorphine solution is absorbed systemically (Weinberg et al., 1988; Mendelson et al., 1997a; Nath et al., 1999; Schuh and Johanson, 1999). When non-dependent subjects with a history of opioid abuse received an acute dose of 4 mg of sublingual buprenorphine solution, peak plasma concentrations occurred at 45 min after the dose (range 30–60 min; Kuhlman et al., 1996).

Distribution of buprenorphine into body fluids and tissues has not been completely characterized. The hepatic extraction of buprenorphine is approximately 1. Buprenorphine is 96% protein bound, binding primarily to alpha and beta globulin (Walter and Inturrisi, 1995). Buprenorphine is highly lipophilic which likely leads to rapid passage across the blood–brain barrier. The high lipophilicity may effect the duration of action (Hambrook and Rance, 1976). The volume of distribution for buprenorphine is 2.5 l/kg. The average maximum plasma concentration after a single 4 mg sublingual solution dose is 3.31 ng/ml (range 1.93–7.19 ng/ml) (Kuhlman et al., 1996). The mean steady-state trough level of buprenorphine during chronic sublingual solution administration of 8 mg/day is 0.8 ng/ml (Kuhlman et al., 1998). In subjects undergoing buprenorphine induction and maintenance, buprenorphine and norbuprenorphine blood levels in the range 0.7–1.0 ng/ml are associated with suppression of opioid withdrawal (Kuhlman et al., 1998).

Buprenorphine is metabolized in the liver by the P450 3A4 enzyme system (Iribarne et al., 1997; Kobayashi et al., 1998). It undergoes N-demethylation to norbuprenorphine and conjugates of both (Cone et al., 1984). The analgesic effect of norbuprenorphine is one-fiftieth that of buprenorphine following intravenous administration (Ohtani et al., 1995), although norbuprenorphine may be a more potent respiratory depressant at local opioid receptors in the lungs (Ohtani et al., 1997). Currently, there is no evidence that norbuprenorphine activity is responsible for effects observed in the treatment of opioid dependence (Ohtani et al., 1995).

About 70% of an intravenous buprenorphine dose is excreted in the feces. Norbuprenorphine has a slower elimination than buprenorphine. Buprenorphine and its glucuronide metabolite appear in the urine for 1–2 days, and norbuprenorphine and its glucuronide metabolite appear for 1–4 days (Cone et al., 1984; Blom and Bondesson, 1985). Urine testing for opiates typically screens for morphine, and these tests do not cross-react with buprenorphine or norbuprenorphine.

### 2.3. Bioavailability

Because buprenorphine has poor oral bioavailability, sublingual administration has been the primary route used in studies of clinical efficacy for treating opioid dependence. Initial clinical trials used a 1-ml alcohol-based solution (typically either 30 or 40% alcohol) but this formulation is not available for routine clinical use. More recent studies have focused on the use of a buprenorphine-containing tablet. There may be an important difference in the bioequivalence of sublingual solution and sublingual tablets. While some authors have reported that the tablets only provide about 50–70% of the corresponding sublingual solution dose (Mendelson et al., 1997a; Nath et al., 1999; Ajir et al., 1999; Schuh and Johanson, 1999), a more recent study found the combination tablet and solution formulations produce buprenorphine blood levels that are not significantly different under chronic dosing conditions (Strain et al., 2002a). Because of buprenorphine’s high lipid solubility, it is also expected to be active by the intranasal route (Lindhardt et al., 2000).

### 2.4. Cross tolerance and blockade

Buprenorphine readily cross-substitutes in individuals dependent on opioids (e.g. heroin, morphine, hydromorphone) and suppresses symptoms of withdrawal from these compounds (Jasinski et al., 1983, 1984; Kosten and Kleber, 1988; Johnson et al., 1989). Repeated sublingual administration of buprenorphine can produce sufficient cross tolerance to block the effects of parenterally administered opioids (Bickel et al., 1988a,b; Rosen et al., 1994; Amass et al., 1996;
Strain et al., 1997). Buprenorphine has been shown to produce dose-related blockade for the solution (in the dose range 2–16 mg/day; Bickel et al., 1988a; Rosen et al., 1994; Schuh et al., 1999), monotherapy tablet (8 and 16 mg; Comer et al., 2001) and combination tablet (up to 32/8 mg/day; Strain et al., 2002b) formulations, when subjects are challenged with prototypic mu agonist opioids such as hydromorphone (2–12 mg; Bickel et al., 1988a; Rosen et al., 1994; Schuh et al., 1999; Strain et al., 2002b) and heroin (0–25 mg; Comer et al., 2001).

2.5. Suppression of spontaneous opioid withdrawal

Single sublingual doses of buprenorphine solution in the range 2–4 mg will attenuate or eliminate signs of withdrawal for 24 h in street heroin addicts, and in individuals who have been abruptly withdrawn from maintenance on 60 mg of daily morphine. At higher doses (acute doses greater than 8 mg of sublingual solution), suppression of withdrawal can increase to 72 h in patients abstaining from illicit opioid use (Eissenberg et al., 1997; Chawarski et al., 1999; Bickel et al., 1999). After patients are stabilized on buprenorphine, suppression of withdrawal can be increased to 48, 72, or 96 h by doubling, tripling, or quadrupling the patient's maintenance dose. This has been demonstrated using both buprenorphine solution (Amass et al., 1994a, 1998; Petry et al., 2000a; Bickel et al., 1999) and buprenorphine/naloxone combination tablets (Amass et al., 2000b, 2001).

2.6. Antagonist properties

As noted above, because of its partial-agonist properties, buprenorphine can precipitate signs and symptoms of opioid withdrawal in some patients physically dependent on opioids. In opioid-dependent individuals, buprenorphine at low doses will substitute for other opioids (i.e. function as an opioid agonist). However, under appropriate conditions buprenorphine at high doses can precipitate an opioid withdrawal syndrome (Kosten and Kleber, 1988; Kosten et al., 1991; Strain et al., 1995; Walsh et al., 1995a; Clark et al., 2002). These signs and symptoms of precipitated withdrawal by buprenorphine are qualitatively similar but quantitatively dissimilar from those produced by a full antagonist such as naltrexone or naloxone. Higher doses of buprenorphine are required to produce antagonist effects equivalent to low doses of naloxone or naltrexone in both chronic and acute physical dependence paradigms (Jasinski et al., 1984; Walsh et al., 1995a; Eisenberg et al., 1996; Gourarier et al., 1996; Schuh et al., 1999).

The degree of withdrawal precipitated by buprenorphine in opioid-dependent individuals is determined by the dose of buprenorphine, dose of maintenance opioid, and time since last dose of maintenance opioid (Jasinski et al., 1984; Strain et al., 1992, 1995; Walsh et al., 1995a; Schuh et al., 1996). Patients dependent on methadone 60 mg/day (but not 30 mg/day) show a significant increase in total withdrawal scores following an acute 8 mg sublingual solution dose of buprenorphine when administered 40 h after the last methadone dose (Walsh et al., 1995a). In patients maintained on methadone 30 mg/day, intramuscularly administered doses of buprenorphine (0.5–8 mg) do not precipitate opioid withdrawal when buprenorphine is administered 20 h after the last dose of methadone (Strain et al., 1992). However, they do produce mild antagonist-like effects when administered 2 h following the maintenance dose of methadone (Strain et al., 1995). In another study, subjects maintained on daily oral methadone (25–45 mg/day, mean 35 mg), and abruptly transferred to 2 mg of daily sublingual buprenorphine solution, showed mild withdrawal symptoms (Jasinski et al., 1984). This probably reflects that the low dose of buprenorphine used only partially suppressed methadone withdrawal rather than precipitated withdrawal.

2.7. Physical dependence potential

Buprenorphine produces physical dependence as demonstrated by the ability of high doses of naloxone and naltrexone to precipitate an opioid withdrawal syndrome in patients maintained on buprenorphine. This profile of physical dependence effects is consistent with an agonist medication having high affinity and low intrinsic activity at the mu opioid receptor. Thus, doses of naloxone (< 3 mg/70 kg) and naltrexone (< 1 mg/70 kg), that would typically be expected to precipitate an opioid withdrawal syndrome in heroin, morphine, and methadone dependent patients, do not produce significant signs and symptoms of opioid withdrawal in buprenorphine-maintained patients. However, higher doses of naloxone and naltrexone will produce signs and symptoms of opioid withdrawal in subjects maintained on 8 mg/day of sublingual buprenorphine solution (Kosten et al., 1990; Eisenberg et al., 1996).

2.8. Pharmacologic characteristics of the buprenorphine/naloxone tablet

Because buprenorphine has poor oral bioavailability, clinical use for opioid dependence treatment is via the sublingual route. As discussed previously, initial studies used a sublingual solution, but attention then focused upon the development of a sublingual tablet (Chiang and Hawks, 1994; Chiang et al., 1996). Tablets may be more easily dispensed, provide more accurate unit dosing, increase dosage stability and are more familiar delivery mechanism than sublingual solution. However, both sublingual solution and tablets could be abused—
solution by direct injection, and tablets by dissolving and injecting. Intranasal abuse of crushed tablets is also possible given buprenorphine’s high lipid solubility and nasal bioavailability (Lindhardt et al., 2000). Anecdotal reports from several countries have described abuse of analgesic formulations of buprenorphine liquid (O’Connor et al., 1988; Morrison 1989; Singh et al., 1992) and tablet preparations (Strang, 1991; Robinson et al., 1993). Reports of intravenous misuse of high dose monotherapy buprenorphine tablets have also emerged from France, where it has been available by prescription from general practitioners since 1996 (Obadia et al., 2001; Thirion et al., 2001). In order to decrease abuse and misuse, a combination buprenorphine/naloxone product has been developed that should have a lower abuse liability compared with buprenorphine alone. The addition of naloxone, with its relatively poor sublingual bioavailability, results in a predominant buprenorphine effect when the combination tablet is taken by the therapeutic (i.e. sublingual) route (Stoller et al., 2001). However, abuse via the parenteral route results in a predominant naloxone effect (Mendelson et al., 1996, 1997b, 1999; Fudala et al., 1998; Stoller et al., 2001).

It was determined that the optimal combination is a 4:1 ratio of buprenorphine to naloxone (see Mendelson and Jones, 2003), and tablets containing 2/0.5 and 8/2 mg of buprenorphine/naloxone have been developed. A human laboratory study of buprenorphine/naloxone has shown doses up to 16/4 mg of buprenorphine/naloxone tablets taken sublingually produce minimal opioid antagonist effects in opioid-dependent subjects (Stoller et al., 2001). However, when buprenorphine/naloxone is delivered parenterally, opioid-dependent subjects experience precipitated withdrawal (Mendelson et al., 1996, 1997b, 1999; Fudala et al., 1998; Stoller et al., 2001). Thus, the addition of naloxone to buprenorphine tablets at doses relevant to clinical treatment should result in decreased abuse potential in certain opioid-dependent populations (e.g. active heroin users and methadone-maintained populations). However, it is important to note that naloxone should not exert a meaningful pharmacologic deterrent effect in non-dependent opioid abusers or in patients already maintained on buprenorphine (Comer and Collins, 2002b; Harris et al., 2000a,b; Strain et al., 2000; Amass et al., 2000c).

3. Starting the patient on buprenorphine

3.1. Overview

Buprenorphine is available as tablets containing either buprenorphine alone (sometimes referred to as monotherapy tablets) or combined with naloxone (combination therapy tablets). It is expected that patients maintained on buprenorphine will be given the tablet containing both buprenorphine and naloxone. Experience from two national evaluations of the combination therapy tablet suggests that direct induction with combination therapy is acceptable to a majority of street heroin users (L. Amass, personal observation). However, for a patient taking a long acting full opioid agonist, monotherapy tablets could be considered for the first 2 days of induction (Amass et al., 2000b, 2001). This section describes starting a patient using the buprenorphine alone tablet. The procedure is the same when starting the patient on the buprenorphine/naloxone combination tablet.

In addition to the possibility of naloxone-related precipitated withdrawal, buprenorphine could also precipitate withdrawal since it is a partial mu agonist opioid. Therefore, prior to administering the initial buprenorphine dose, consideration should be given to three important factors. These factors include: (1) the time since last opioid use (theoretically, a partial agonist opioid should be most effective and demonstrate the least antagonist effects when the patient is experiencing slight opioid withdrawal); (2) the type of opioid dependence (i.e. long- or short-acting opioid); and (3) the degree or level of opioid physical dependence. The shorter acting the opioid of dependence, the longer time since last opioid use, and the lower the level of physical dependence, the higher the initial dose can be. Each of these factors will be considered in more detail here (for further review, see Bickel and Amass, 1995).

3.2. Time since last dose

The likelihood of a buprenorphine- or buprenorphine/naloxone-induced precipitated withdrawal increases as the time interval since last opioid ingestion decreases. Mild precipitated withdrawal has been observed at a time interval of 2 h since last opioid dosing (Strain et al., 1995). Because of this potential, patients transferring from short-acting opioids (i.e. street heroin) should be instructed to abstain from illicit opioid use for at least 4 h prior to administration of the first buprenorphine dose. If the patient’s drug use history is vague or inconsistent, or if acute opioid effects are suspected, the first dose should be delayed for at least 4 h or until mild withdrawal signs or symptoms are observed or reported.

3.3. Half-life of opioid used

Induction onto buprenorphine from short-acting opioids such as heroin should be easy to accomplish, and reports of buprenorphine-induced precipitated withdrawal in abusers dependent upon heroin have been extremely uncommon. Induction onto buprenorphine from long-acting opioids can be more problematic, possibly due to kinetic differences in long- and
short-acting full mu-opioid agonists. A longer time interval between methadone and subsequent buprenor-
phine dosing is recommended depending on the dose of methadone. In controlled studies of subjects maintained
on 20–40 mg of daily methadone, the transition to buprenorphine is less difficult and can generally be
initiated 24 h after the last dose of methadone (Law et al., 1997; Harris et al., 2000a,b). Successful titration
initiated 24 h after the last dose of methadone (Law et al., 2002). For higher doses of methadone, the transition to buprenorphine may be made more tolerable by delaying initiation of buprenorphine therapy for more than 24 h after the last dose of methadone (Bouchez et al., 1998) or rapidly lowering the dose of methadone and offering supportive therapy with ancillary medications prior to buprenorphine induction (Levin et al., 1997).

3.4. Amount of opioid drug use

It may be possible to precipitate an opioid withdrawal syndrome if the level of physical dependence and initial
dose of buprenorphine are high. For example, patients with a level of physical dependence on long-acting
opioids equivalent to > 40 mg/day of methadone should ideally reduce their opioid use to the equivalent of 40
mg/day or less of methadone prior to initiating buprenorphine therapy. While some patients with higher
levels of daily opioid use can be inducted onto buprenorphine safely provided they are abstinent for a
sufficient time period to result in clinically apparent withdrawal symptoms (Levin et al., 1997; Amass et al.,
2000b, 2001; Lintzeris, 2000), these patients should be prepared in advance for the possibility of some mild
discomfort during the first few days of buprenorphine induction.

3.5. Initial dose of buprenorphine

After taking a clinical history that includes time since
last opioid use, and type and amount of opioid used, the
appropriate initial dose of buprenorphine can be
selected. An initial dose of buprenorphine 4 mg or
buprenorphine/naloxone 4/1 mg is recommended fol-
lowed in 3–4 h with additional dose of up to 4 mg (or 4/
1 mg) if indicated. On subsequent days, the dose of buprenorphine/naloxone should be increased to 12/3–
16/4 mg/day. During this period of dose induction, patients may need to attend the clinic or doctor’s office
on a daily basis for dose adjustment and clinical monitoring. Table 1 provides guidance for selecting the
optimal dose of buprenorphine based on the patient’s self-reported opioid use.

If there is concern for possible precipitation of an
opioid withdrawal syndrome, the first daily dose can be
split with the second half administered 3–4 h after the
first dose. In most studies, the starting dose of bupre-
orphine administered on the first day has been 2 mg of
sublingual solution. However, single doses of buprenor-
phine up to 4 mg tablet can be administered without
undue concern for causing an opioid withdrawal syn-
drome in opioid-dependent patients.

Induction onto a dose as high as 16 mg of buprenor-
phine solution has been accomplished by administering
2, 4, 8, and 16 mg of buprenorphine on days 1–4,
respectively (Ling et al., 1998). A similar induction
schedule using buprenorphine combination tablets
would be 4/1, 8/2, 12/3, 24/6 mg on days 1–4. However,
the objective of induction should be to achieve a
maintenance dose (i.e. 16 mg) as rapid as possible (i.e.
within 2–3 days).

3.6. Switching to buprenorphine/naloxone

Patients receiving buprenorphine alone can be
switched easily to the buprenorphine/naloxone combi-
nation tablet. This transition can be made by simply
changing the patient to the corresponding equivalent
dose (i.e. if taking 16 mg/day, then immediately change
to 16/4 mg/day of buprenorphine/naloxone). However,
in most cases induction can be accomplished with
immediate use of buprenorphine/naloxone, bypassing
initial buprenorphine monotherapy use (see Section 3.1).

4. Maintaining the patient on buprenorphine

4.1. Overview

Numerous studies have tested the efficacy and safety
of buprenorphine during relatively short (i.e. 1 year or
less) maintenance treatment episodes (e.g. Johnson et
al., 1992, 2000; Kosten et al., 1993; Strain et al., 1994;
Ling et al., 1996; Schottenfeld et al., 1997, 2000;
Uehlinger et al., 1998; Fischer et al., 1999; Mattick et
al., 1999; Pani et al., 2000; Amass et al., 2000a; Petitjean
et al., 2001; Perez de los Cobos et al., 2000; Ahmadi,
2002). Most of these studies have been conducted on an
outpatient basis, compared buprenorphine with metha-
done, used a liquid form of buprenorphine rather than
tables (except for the reports by Uehlinger et al., 1998;
Fischer et al., 1999; Mattick et al., 1999; Pani et al.,
2000; Petitjean et al., 2001; Amass et al., 2000a; Ahmadi,
2002), and tested buprenorphine alone (except for the
report by Amass et al., 2000a that evaluated the tablet
combined with naloxone). In general, these studies have
shown that daily doses of 8 mg of sublingual solution or
16 mg tablet are safe, well tolerated, and equivalent to
approximately 60 mg/day of oral methadone.

As a partial agonist, higher doses of buprenorphine
may not produce corresponding increases in effects
(such as a subjective sense of high). However, higher doses may provide better cross-tolerance to other opioids over longer periods of time. Thus, it may be the case that increasing the dose of buprenorphine at some point will produce no appreciable difference in the patient’s subjective effects, but may provide further efficacy in blocking the effects of illicit opioids and hence reduce illicit opioid use. It is theoretically possible for effects of buprenorphine (which are perceived as positive by the patient) to decrease as the dose of buprenorphine is increased (a phenomenon sometimes called interoceptive withdrawal). Consistent with this possibility, among patients treated with 16 mg/day of buprenorphine in a double-blind study and given the opportunity to increase their dose to 32 mg/day during an extension open-label phase of the study, approximately 20% requested a dose decrease back to 16 mg/day after receiving the 32 mg/day dose (W. Ling, personal communication 31 August 2002 and Paul Bevan, Reckitt Benckiser, written communication 4 August 1999). Therefore, much higher doses of sublingual buprenorphine tablets (e.g. in excess of 32 mg/day) may not be as readily acceptable to some patients, even though further blockade effects may occur.

4.2. Optimal daily dose of buprenorphine

This section reviews issues pertinent to maintaining the opioid-dependent patient on buprenorphine. As is the case with other medications for medical conditions, ultimate dosing considerations depend upon the individual circumstances of patients. Thus, while conclusions

<table>
<thead>
<tr>
<th>Generic name (brand name)</th>
<th>Unit of use, dose (mg)</th>
<th>Self-reported drug use (four times per day)</th>
<th>Morphine equivalent parenteral dose (mg), total daily (four times per day)</th>
<th>Methadone equivalent oral dose (mg), daily</th>
<th>Buprenorphine equivalent sublingual tablet dose (mg), daily</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oxycodone</strong>&lt;sup&gt;a,b&lt;/sup&gt; (Percocet, percocan roxiconodone, oxylr)</td>
<td>5</td>
<td>6–9 2–3</td>
<td>40–60 (10–15)</td>
<td>20–30</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>4</td>
<td>80 (20)</td>
<td>40</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>15–18</td>
<td>5–6</td>
<td>100–120 (25–30)</td>
<td>50–60</td>
<td>16</td>
</tr>
<tr>
<td><strong>Hydrocodone</strong>&lt;sup&gt;a,b&lt;/sup&gt; (Hycodan, others)</td>
<td>5</td>
<td>6–9 2–3</td>
<td>40–60 (10–15)</td>
<td>20–30</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>4</td>
<td>80 (20)</td>
<td>40</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>15–18</td>
<td>5–6</td>
<td>100–120 (25–30)</td>
<td>50–60</td>
<td>16</td>
</tr>
<tr>
<td><strong>Codeine</strong>&lt;sup&gt;c&lt;/sup&gt; (Demerol)</td>
<td>15</td>
<td>13–20 9–14</td>
<td>40–60 (10–15)</td>
<td>20–30</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>26</td>
<td>18</td>
<td>80 (20)</td>
<td>40</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>33–40</td>
<td>22–28</td>
<td>100–120 (25–30)</td>
<td>50–60</td>
<td>16</td>
</tr>
<tr>
<td><strong>Meperidine</strong>&lt;sup&gt;c&lt;/sup&gt; (Demerol)</td>
<td>50</td>
<td>6–9 2–3</td>
<td>40–60 (10–15)</td>
<td>20–30</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>4</td>
<td>80 (20)</td>
<td>40</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>15–18</td>
<td>5–6</td>
<td>100–120 (25–30)</td>
<td>50–60</td>
<td>16</td>
</tr>
<tr>
<td><strong>Hydromorphone</strong>&lt;sup&gt;d&lt;/sup&gt; (Dilaudid)</td>
<td>2</td>
<td>2</td>
<td>40–60 (10–15)</td>
<td>20–30</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>1–2</td>
<td>80 (20)</td>
<td>40</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>5–6</td>
<td>2–3</td>
<td>100–120 (25–30)</td>
<td>50–60</td>
<td>16</td>
</tr>
<tr>
<td><strong>Morphine</strong>&lt;sup&gt;c&lt;/sup&gt;</td>
<td>15</td>
<td>4–6 1</td>
<td>40–60 (10–15)</td>
<td>20–30</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>1–2</td>
<td>80 (20)</td>
<td>40</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>10–12</td>
<td>2</td>
<td>100–120 (25–30)</td>
<td>50–60</td>
<td>16</td>
</tr>
<tr>
<td><strong>Heroin</strong>&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Bag&lt;sup&gt;e&lt;/sup&gt;</td>
<td>4–6 0.25</td>
<td>40–60 (10–15)</td>
<td>20–30</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>0.50</td>
<td>80 (20)</td>
<td>40</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>10–12</td>
<td>1.00</td>
<td>100–120 (25–30)</td>
<td>50–60</td>
<td>16</td>
</tr>
</tbody>
</table>

This table includes selected common opioid agonist medications which patients may report abusing. The first column describes each medication by generic name with superscripts for references (see below) used to estimate relative analgesic potency and/or comparable (oral vs. parenteral) steady-state blood levels. Selected brand names are noted in parentheses. The second column lists the milligrams of medication per unit of use which could be either tablets, capsules, caplets, bags, etc. Self-reported drug use is the number of units per use with the assumption that use is four times per day (i.e. multiply units by a factor of 4 for daily use). Next, morphine equivalents are calculated based on four times per day use. Morphine doses are then converted to daily methadone doses. The daily dose of buprenorphine is based on current data from controlled clinical trials and laboratory studies comparing methadone and buprenorphine. Note: Relative analgesic potencies are based on acute and not chronic dosing, as is the case when treating opioid dependence.

<sup>a</sup> Jasinski, 1977.
<sup>b</sup> Agency for Health Care Policy and Research, 1994.
<sup>c</sup> Jaffe and Martin, 1990.
<sup>d</sup> Vallner et al., 1981.
<sup>e</sup> Units are based on bag weighing 100 mg and 15% pure heroin.
from studies can provide guidance to the clinician, each patient’s personal drug use history must be considered when using buprenorphine in the treatment of opioid dependence.

For most patients, an initial target dose should be 12/3–16/4 mg of daily sublingual combination tablet. If patients continue to have evidence of illicit opioid use or withdrawal while maintained on a daily dose of 16 mg of buprenorphine, then the dose should be increased. The minimum dose increase possible is increments of 2 mg buprenorphine with 0.5 mg of naloxone. Splitting of tablets is not recommended, as they are not scored and do not break cleanly. As is the case when using other opioid agonist medications, a period of time should elapse between dose changes in order to determine clinical response. If the therapeutic target is suppression of opioid withdrawal, then dose changes may occur on a near daily basis. If the therapeutic target is suppression of illicit opioid use, then dose changes may occur less frequently (e.g. on a weekly or biweekly basis), since clinical response may be slower to detect. Moreover, the degree and frequency of adjunct psychosocial services available will also impact a patient’s ability to refrain from illicit opioid use and should also be taken into consideration when contemplating dose changes.

4.3. What to do if illicit opioid use continues

Patients maintained on buprenorphine may have evidence of continued illicit opioid use. In such cases, the first step is to determine that the patient is ingesting the medication properly. It is important to clearly explain to the patient that tablets are not to be swallowed, and that they are to be held under the tongue until fully dissolved. When a specific dose requires the use of multiple tablets, the patient should be advised to place all the tablets under his/her tongue at one time. If more than two tablets are required and it is uncomfortable for the patient to place all the tablets under his/her tongue at one time, they should be advised to place two tablets at a time under the tongue. Patients should be instructed that swallowing the tablet, or parts of the tablet, results in inactivation of the medication and essentially no therapeutic effect. This usually motivates patients to comply with the sublingual procedure.

Another possible reason a patient may continue to use illicit opioids is because they are receiving an inadequate dose of buprenorphine. The use of an inadequate dose will generally occur earlier in treatment. A dose increase would be indicated if the patient is showing withdrawal symptoms or complains of an inadequate dose.

A third reason may be the development of tolerance. Tolerance may develop later in treatment, and occurs when it takes a higher dose to get the same effect as previously observed with a lower dose. Although tolerance has not been demonstrated in patients treated with buprenorphine, this is not uncommon for patients maintained on other opioids.

Finally, patients may continue to use illicit opioids even when they are compliant in taking high doses of any opioid agonist medication. Like other pharmacotherapies for substance abuse disorders (i.e. methadone for opioid dependence, nicotine for smoking), optimal treatment outcome with buprenorphine will probably occur when buprenorphine is combined with non-pharmacologic treatments (e.g. individual counseling, group therapies, behavioral incentive programs including contingency contracting) (Bickel et al., 1997). It is especially important to consider these non-pharmacologic interventions when addressing continued illicit opioid use, or any drug use, in patients maintained on adequate doses of buprenorphine.

4.4. Less-than-daily dosing of buprenorphine

Once a patient is stabilized on daily buprenorphine dosing, it may be possible to switch him/her to a less-than-daily dosing schedule. It has been shown that plasma levels of buprenorphine and its metabolites at 72 h following a 32 mg dose of solution are higher than plasma levels observed at 24 h following an 8 mg dose of buprenorphine solution (Walsh et al., 1994), and that doses ranging from 16 mg/70 kg to 44 mg/70 kg result in dose-related increases in plasma levels at 24, 48 and 72 h following the buprenorphine dose (Chawarski et al., 1999). Thus, increasing the dose of buprenorphine increases the amount of buprenorphine in the body, and doses equivalent to $\geq 8–16$ mg of solution should increase the duration of effects and allow for a longer time period between doses (i.e. 48–72 h). Patients maintained on 8 mg of daily sublingual solution, and who are free of illicit opioid use, have been shown to tolerate a 72 h dose omission well (Eisenson et al., 1997).

Several studies have tested the efficacy of a buprenorphine sublingual solution on an alternate-day basis (Fudala et al., 1990; Amass et al., 1994a, 1998; Johnson et al., 1995b; Bickel et al., 1999). The buprenorphine/naloxone combination tablet has also been evaluated for this purpose (Amass et al., 2000b). Buprenorphine sublingual solution (Resnick et al., 1994; O’Connor et al., 1996, 1998; Schottenfeld et al., 2000; Johnson et al., 2000), the buprenorphine alone tablet (Perez de los Cobos et al., 2000) and buprenorphine/naloxone combination tablets (Amass et al., 2001) have been tested on a Monday/Wednesday/Friday schedule. Alternate-day and Monday/Wednesday/Friday schedules are preferred to daily dosing schedules by buprenorphine-maintained outpatients (Amass et al., 1998, 2001). A more limited set of studies have examined buprenorphine sublingual solution on a 96 h dosing schedule by administering
quadruple the daily maintenance dose of buprenorphine every fourth day (Petry et al., 1999, 2000a). In an open-label study, a 96 h schedule was preferred to more frequent dosing schedules by a small subset of abstinent patients who completed an initial double-blind portion of the study (Petry et al., 2000a). Every fifth day dosing schedules have also been examined (Petry et al., 2001; Gross et al., 2001), although due to reports of increased withdrawal during the extended inter-dosing interval, this schedule is not recommended for clinical use.

Tripling of the daily dose can be well-tolerated and allows for a 72 h dose interval (Bickel et al., 1999; Petry et al., 1999; Amass et al., 2001). While every-other-day dosing is acceptable to patients, the availability and equivalent acceptability of thrice-weekly dosing will probably preclude its common clinical use. Currently, it would be best to recommend a thrice-weekly schedule, although additional studies of twice weekly (e.g. Monday and Thursday) dosing may show this schedule is equally effective and also liked by patients.

For patients on daily buprenorphine who are switching to thrice-weekly buprenorphine, doses ingested on medication days should be increased to compensate for the longer time period between doses. Most studies have suggested that the total dose taken on an active dosing day should equal the amount taken over the corresponding time interval during daily dosing (Amass et al., 1994a, 1998, 2000b, 2001; Bickel et al., 1999; Johnson et al., 2000; Perez de los Cobos et al., 2000). Another suggestion is for the total weekly dose of buprenorphine given during daily dosing to be equal to that given during Monday/Wednesday/Friday dosing (Schottenfeld et al., 2000).

Because buprenorphine is a partial agonist, maximum agonist effects (depending on the effect measured) are below that expected for a full agonist. Thus, increases in the daily dose are safe (i.e. minimal risk of an opioid overdose) and well tolerated by patients. The transition from daily dosing to thrice-weekly dosing is possible with an abrupt transition that should probably begin on a Monday. Thus, a patient maintained on 8/2 mg of daily buprenorphine/naloxone could receive that dose on a Sunday, then receive 16/4 mg on Monday, skip Tuesday, receive 16/4 mg on Wednesday, skip Thursday, and then receive 24/6 mg on Friday. Patients should initially be monitored after acute doubling of their dose to ensure that excessive opioid agonist effects do not occur. However, a study of buprenorphine alone showed that patients maintained on 8 mg of daily sublingual solution could receive acute doses of up to 16 mg of parenteral buprenorphine and not experience excessive acute opioid agonist-like effects (Strain et al., 1997).

Buprenorphine is approved by the Food and Drug Administration to be administered sublingually as a single daily dose. Under the Drug Addiction Treatment Act (2000), a physician in office-based practice can prescribe buprenorphine for opioid-dependent patients to take at home. Prescriptions for buprenorphine must be written and dispensed consistent with federal and state law for writing, filling, and filing schedule III medications. Under the DATA, states cannot preclude practitioners from prescribing or dispensing buprenorphine or buprenorphine/naloxone for the treatment of opioid dependence unless the state specifically passes a law prohibiting or specially regulating such activity. Currently we are unaware of any state that has taken such action; however, practitioners should be aware of this possibility. The availability of buprenorphine through traditional prescription practice makes the need for less-than-daily dosing less critical for reducing barriers to treatment (i.e. reduced clinic visits, etc.). However, when the diversion of buprenorphine for non-therapeutic purposes (e.g. intravenous administration, selling) is suspected, the medical staff may wish to ensure compliance by using a less-than-daily dosing protocol. Such a protocol could ensure compliance with observed dosing and no take-home medications but still reduce the burden of daily clinic visits both in office-based practice and opioid treatment programs. There may also be special situations (e.g. travel) where less-than-daily dosing is advantageous for the patient.

4.5. Side effects during maintenance treatment

Buprenorphine as a solution, tablet and combination tablet (i.e. buprenorphine/naloxone) has been tested in over 5000 patients in the US for the treatment of opioid dependence. It has been well tolerated with no apparent significant side effects. Like other opioids, it produces typical opioid-like side effects such as constipation. Increases in liver enzymes (AST and ALT) have been observed in individuals receiving buprenorphine (Lange et al., 1990; Petry et al., 2000b). There have been 53 cases of buprenorphine associated cytolytic hepatitis reported in France since buprenorphine was introduced as a treatment for opioid dependence in 1996 (Auricoome et al., in press). An association between intravenous buprenorphine misuse and liver toxicity has also been reported in some patients that is believed to likely be due to the increased bioavailability of buprenorphine when taken parenterally (Berson et al., 2001).

4.6. Buprenorphine overdose

Because of the bell-shaped dose–response curve observed with buprenorphine (Fig. 2), it is possible that an overdose of buprenorphine will produce fewer mu agonist opioid effects than a more moderate dose. Indeed, preclinical work suggests respiratory depression decreases with higher doses of buprenorphine (Doxey et al., 1982), and at least one case report of buprenorphine overdose found no significant adverse effects such as
respiratory depression associated with the event (Banks, 1979). However, buprenorphine respiratory depression in subjects not physically dependent upon opioids has been reported (e.g. Thörn et al., 1988; Gal, 1989; Zacny et al., 1997).

If a patient overdoses on buprenorphine and has clinically significant effects such as respiratory depression, high dose naloxone hydrochloride (10–35 mg/70 kg) may be of limited value in the management of the overdose (Kosten et al., 1990; Eissenberg et al., 1996). Buprenorphine is longer acting than the opioid antagonist naloxone. Therefore, in cases of suspected buprenorphine overdose the patient should be closely monitored with life support measures (i.e. re-establishment of adequate ventilation with mechanical assistance of respiration if necessary) until they regain stability. The use of the opioid antagonist naloxone to reverse buprenorphine agonist effects has not been reported.

It is important to note that following the introduction of buprenorphine monotherapy tablets in France in 1996, where it is available by prescription from general practitioners under minimal regulatory restrictions, a series of overdose deaths were reported. The vast majority of these cases resulted when buprenorphine and benzodiazepines were concomitantly abused via the parenteral route (Reynaud et al., 1998; Tracqui et al., 1998a,b; Kintz, 2001, 2002), although at least one case report describes a fatal buprenorphine intoxication associated with oral benzodiazepine ingestion (Gaulier et al., 2000). Of all reported overdose deaths with buprenorphine in France, only two cases of buprenorphine alone overdose deaths have been reported and these two cases died of Mendelson’s syndrome (i.e. asphyxiation due to aspirating vomitus, Kintz, 2002). Although buprenorphine with naloxone tablets are not currently available in France, post-marketing surveillance data of the buprenorphine monotherapy product indicates that the rate of these overdose deaths has been decreasing following these reports (personal communication with Doug DeShong, Schering-Plough, August 2000). Moreover, the death rate from overdose with buprenorphine is still far less than that associated with methadone (Auriacombe, 2001). In France between 1994 and 1998, estimates of the yearly death rate from methadone was at least three times greater than buprenorphine, although the absolute number of buprenorphine-related deaths was greater given that fourteen times more patients received buprenorphine than methadone during this period (Auriacombe, 2001).

Certainly, educating patients about the potential lethality of abusing buprenorphine in combination with respiratory depressants (especially benzodiazepines) will be extremely important. Therefore, patients being treated with take-home doses of buprenorphine will need to be cautioned regarding the danger of combining buprenorphine with benzodiazepines and other central nervous system depressants (e.g. alcohol).

4.7. The importance of concurrent non-pharmacologic treatment during maintenance

While the emphasis in this review has been on the use of buprenorphine as a medication, it is important to point out that optimal outcomes with buprenorphine treatment will probably occur when non-pharmacologic services are intimately linked to buprenorphine treatment (e.g. Bickel et al., 1997). Other medications for substance abuse disorders, such as nicotine substitution products for smoking cessation, methadone for opioid dependence, and naltrexone for alcoholism, all appear to have better outcomes when medication treatment is combined with non-pharmacologic services. Buprenorphine is available through non-opioid treatment programs, such as physician office-based primary care practice (Fiellin et al., 2001; O’Connor et al., 1996, 1997, 1998; Resnick et al., 2001; Drug Addiction Treatment Act, 2000; Vignau et al., 2001; Thiron et al., 2002), and it is important for clinicians to develop mechanisms to deliver effective, concurrent non-pharmacologic services that maximize the outcome associated with use of buprenorphine.

5. Reducing/discontinuing buprenorphine

5.1. Overview

While numerous outpatient clinical trials have tested the efficacy of maintenance buprenorphine, there have been relatively few controlled systematic studies of buprenorphine medical withdrawal (“detoxification” or “dose reduction”). For a complete review of this topic, see Gowing et al. (2002). Abrupt discontinuation of buprenorphine appears to produce a mild to moderate withdrawal syndrome (Jasinski et al., 1978, 1983; Seow et al., 1986; Kosten and Kleber, 1988; Fudala et al., 1990; San et al., 1992). After abrupt discontinuation of buprenorphine, subjective symptoms of opioid withdrawal begin within the first 3 days, peak between days 3 and 5 and after cessation of buprenorphine, and return to baseline in 10–14 days (Fudala et al., 1990; San et al., 1992). The profile of withdrawal effects observed with buprenorphine is different from that observed with other opioid agonists (Jasinski et al., 1978; Mello and Mendelson 1980; Mello et al., 1982; Fudala et al., 1990). Autonomic signs of opioid withdrawal (e.g. chills, gooseflesh, tremors, rhinorrhea, lacrimation) are generally less pronounced with buprenorphine than with full mu-opioid agonists, although these signs may be present (typically in the first 5 days after abrupt discontinuation). Sleep disturbance can persist for
longer than 5 days in patients who abruptly stop buprenorphine treatment (Fudala et al., 1990; San et al., 1992).

While the focus of this review is on the use of sublingual buprenorphine in the outpatient maintenance treatment of opioid dependence, parenteral buprenorphine has been used for relatively rapid (less than 1 week) opioid withdrawal, typically on an inpatient basis. The following section reviews the use of buprenorphine for opioid withdrawal on an outpatient basis, then briefly discusses the use of buprenorphine for more rapid withdrawals on an inpatient basis.

5.2. Outpatient treatment of opioid withdrawal with buprenorphine

Examples of possible outpatient dose reduction schedules using equal reductions (i.e. 2 mg increments) or 50% buprenorphine dose reduction schedules are shown in Table 2. Although reports and clinical experience suggest that buprenorphine can be used for relatively short withdrawal periods (3–14 days) for inpatient use, the short-term use of buprenorphine in an outpatient setting has not been extensively investigated (O’Connor et al., 1997; Diamant et al., 1998; Lintzeris, 2002). However, there are several outpatient clinical trials comparing buprenorphine to methadone during maintenance (described above), which also included withdrawal phases at the end of the studies. The study designs, as reported, suggest the withdrawal phases were of several weeks duration, and differential attrition by condition during maintenance phases limits the conclusions that could be drawn about the relative efficacy of buprenorphine during withdrawal. One report used a dose reduction schedule of 12.5% per week, and found relatively good outcomes during initial dose reductions but then significantly increased rates of illicit opioid use when patients were finally switched to placebo (Mudric et al., 1998).

The first randomized controlled outpatient medical withdrawal (i.e. detoxification, dose taper) study compared oral methadone 30 mg and sublingual buprenorphine solution 2 mg (Bickel et al., 1988b). The study included 45 subjects maintained on study medication for 3 weeks followed by a 4-week dose taper and 6 weeks of placebo. The drop out rate and use of illicit opiates was high in both groups, suggesting that a longer dose taper might be more optimal. Another outpatient randomized clinical trial was expressly designed to systematically examine the rate of buprenorphine solution dose reduction and its associated withdrawal. This study compared a 1-mg dose reduction every 4 days (a “gradual” procedure over 36 days) to a 50% dose reduction every 4 days (a “rapid” procedure over 12 days) under double-blind conditions, and found superior outcomes for the more gradual dose reduction schedule (Amass et al., 1994b). Another uncontrolled evaluation found that a gradual, 28-day buprenorphine dose reduction retained a majority of subjects through the active phase of dose taper and was associated with low levels of self-reported withdrawal (Becker et al., 2001). Finally, a third randomized clinical study tested the efficacy of buprenorphine for use during a 6-month outpatient dose reduction schedule. This study found that patients receiving buprenorphine and a multi-component behavioral intervention, which included voucher-based contingency management, were two to three times more likely to complete treatment and achieve 8 weeks of continuous opioid abstinence compared with patients receiving buprenorphine with standard counseling (Bickel et al., 1997).

While there have been few controlled studies of buprenorphine dose reduction, general recommendations that have been derived from methadone studies may also apply to the use of buprenorphine (Strain, 1999). Gradual dose reduction is recommended over rapid dose reduction or abrupt cessation since the former has been shown to provide less self-reported withdrawal, increased retention, and less illicit-opioid use. Thus, medical withdrawal of medication with gradual decreases in dose should be optimal. Better outcomes may be achieved if dose changes are made only after patients have been stabilized on their current dose, are aware of their dose schedule, receive advance warning of their dose changes, and have access to more intensive ancillary services.

Table 2
Examples of outpatient detoxification schedules using buprenorphine sublingual tablets

<table>
<thead>
<tr>
<th>Day</th>
<th>Buprenorphine dose (mg), sublingual tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Equal reduction</td>
</tr>
<tr>
<td>1–4</td>
<td>16</td>
</tr>
<tr>
<td>5–8</td>
<td>14</td>
</tr>
<tr>
<td>9–12</td>
<td>12</td>
</tr>
<tr>
<td>13–16</td>
<td>10</td>
</tr>
<tr>
<td>17–20</td>
<td>8</td>
</tr>
<tr>
<td>21–24</td>
<td>6</td>
</tr>
<tr>
<td>25–28</td>
<td>4</td>
</tr>
<tr>
<td>29–32</td>
<td>2</td>
</tr>
<tr>
<td>33–36</td>
<td>0</td>
</tr>
</tbody>
</table>

* Adapted from Amass et al. (1994b).

The number of days at each dose can be extended (e.g. 7 days, etc.) to extend the duration of medical withdrawal (Mudric et al., 1998).

5.3. Inpatient treatment of opioid withdrawal with buprenorphine

Three inpatient studies using sublingual buprenorphine over 10 days or less reported it was effective for withdrawing patients from opioids (Janiri et al., 1994;
Zhi-Min et al., 1997; Vignau, 1998). Additionally, a series of case reports found parenteral doses of buprenorphine for short periods of time (e.g. less than 1 week) were an acceptable and effective means of withdrawing opioid-dependent patients in an inpatient setting (Par-ran et al., 1994) or to treat opioid withdrawal in medically ill hospitalized patients (Welsh et al., 2002). Examples of possible inpatient dose reduction schedules ranging from 3 to 10 days are shown in Table 3.

Three studies have examined the use of buprenorphine compared with clonidine in the inpatient treatment of opioid withdrawal. The first study utilized 10 days of dosing and found sublingual buprenorphine solution was more effective than oral clonidine in relieving opioid withdrawal symptoms in subjects randomized to the two medications (Nigam et al., 1993). The second randomized controlled study also compared sublingual buprenorphine solution to oral clonidine, although treatment periods were shorter (3 days of buprenorphine and 5 days of clonidine; Cheskin et al., 1994). Like in the Nigam et al. study, buprenorphine provided greater relief of opioid withdrawal symptoms. A third randomized controlled study found parenteral buprenorphine superior to clonidine and lefetamine (a structural analog of clonidine) for opioid withdrawal in methadone-maintained patients who had their methadone dose tapered to 10 mg prior to the introduction of buprenorphine (Janiri et al., 1994). These inpatient findings also parallel two other reports supporting the superiority of buprenorphine relative to clonidine (Fingerhood et al., 2001) and lofexidine (White et al., 2001) for outpatient opioid dose reduction.

Finally, one double-dummy, randomized controlled trial compared the buprenorphine monotherapy tablet (starting dose 4 mg) and methadone (starting dose 20 mg) for brief inpatient detoxification of polysubstance abusing opioid addicts (Seifert et al., 2002). Doses of buprenorphine and methadone were tapered over 11 days and also combined with the anticonvulsant carbamazepine (CBZ), delivered simultaneously over 14 days. At the end of the first and second week of treatment, buprenorphine/CBZ-treated patients reported significantly fewer withdrawal symptoms relative to patients treated with methadone/CBZ, and these differences were similarly confirmed by observer reports. This study further supports the use of buprenorphine for the inpatient management of opioid withdrawal.

6. Use of buprenorphine in special populations

6.1. Overview

Few studies have been designed to specifically assess the effects of buprenorphine in special populations. Several studies have reported results in special populations as secondary outcome measures.

6.2. Gender

It is possible there may be differences between men and women in the response to buprenorphine. For example, in one clinical trial it was found that, early in treatment, men had fewer opiate positive urine specimens than women (Johnson et al., 1995a). However, another study found that women treated with a relatively low dose of buprenorphine (4 mg sublingual solution per day) had better outcomes than men, even when controlling for weight (Schottenfeld et al., 1998). However, in the latter study no differences were found between genders for higher daily doses of buprenorphine.

The same concentration of buprenorphine in plasma may produce different levels of effects in men versus women. When buprenorphine is used as an analgesic, women require less buprenorphine than men for pain control although there is no difference between sexes in the plasma concentrations of drug (McQuay et al., 1980). These differences between men and women may reflect differences in hormonal changes, such as cortisol response to buprenorphine (Moore et al., 1981).

The clinical implications of possible gender differences for the effects of buprenorphine need to be better established before recommendations can be made about adjustments in the use of buprenorphine for men versus women. However, this is an area of interest, and these preliminary reports suggest that further attention should be given to the possibility of a gender difference with buprenorphine.

Table 3

Examples of 10 day or less inpatient detoxification schedules using buprenorphine sublingual tablets

<table>
<thead>
<tr>
<th>Day</th>
<th>Buprenorphine dose (mg), sublingual tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10-day schedulea</td>
</tr>
<tr>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>10</td>
<td>0</td>
</tr>
</tbody>
</table>

a Adapted from Vignau (1998).
b Adapted from Zhi-Min et al. (1997).
c Adapted from Cheskin et al. (1994).
6.3. HIV-positive patients

In general, there has been little work looking at differential efficacy of medications for treating opioid dependence in HIV-positive patients. There is one report of two patients positive for HIV treated on an inpatient basis with buprenorphine for opioid withdrawal (Montoya et al., 1995). Both tolerated the medication well, had no significant adverse effects, and successfully completed the withdrawal.

Another report (Marsch et al., 1999) concluded that buprenorphine treatment reduced HIV risk behaviors including frequency of needle use, needle sharing, and drug risk composite scores. Additionally, a study from France (Carrieri et al., 2000) reported no interaction on drug risk composite scores. A study from Germany also demonstrated no interaction on drug risk composite scores. Additional studies of buprenorphine use in humans during pregnancy since its introduction for the treatment of opioid dependence in 1996.

Studies assessing the potential interaction of buprenorphine with HIV antiretroviral therapy are limited. Because buprenorphine is metabolized by cytochrome P450 3A4 (Iribarne et al., 1997; Kobayashi et al., 1998), inhibitors of this enzyme such as the HIV protease inhibitors ritonavir, indinavir and saquinavir may increase plasma concentrations of buprenorphine. One report has described the lack of interaction of buprenorphine and LAAM with zidovudine, unlike methadone that can produce zidovudine toxicity (McCance-Katz et al., 2001).

6.4. Pregnant patients

A full discussion on the use of buprenorphine in the treatment and management of pregnant patients and its effects on the neonate can be found in this review (Johnson et al., 2003). While there are several preclinical (animal) studies on the consequences of buprenorphine use during pregnancy, there have been only three prospective and two open-labeled controlled studies of buprenorphine use in humans during pregnancy. However, there have been a series of case reports, mainly from France, of buprenorphine use during pregnancy since its introduction for the treatment of opioid dependence in 1996.

While buprenorphine is classified in Category C for use in pregnancy (no adequate well-controlled studies in pregnant women), there is continuing interest in designing and conducting controlled human studies to assess the potential use of buprenorphine during pregnancy. It is recommended that buprenorphine only be used during pregnancy if potential benefits justify potential risks.

6.5. Hepatic disease, renal disease

Buprenorphine is metabolized by the liver, and the activity of buprenorphine may be increased and/or extended in individuals with impaired hepatic function or those receiving agents known to decrease hepatic clearance (McQuay and Moore, 1995). Buprenorphine is metabolized by cytochrome P450 3A4 (Iribarne et al., 1997; Kobayashi et al., 1998), so medications that inhibit or induce this enzyme may alter the metabolism of buprenorphine (see Section 6.3). Pregnant women, primarily from France, of buprenorphine use during pregnancy if potential benefits justify potential risks.

In patients with renal failure or renal impairment, there is no significant difference in the kinetics of buprenorphine when compared with normal control populations, although plasma concentrations of norbuprenorphine and buprenorphine-3-glucuronide are increased in patients with renal failure (Summerfield et al., 1985; Hand et al., 1990). Further, buprenorphine is well tolerated in patients with renal disease (Summerfield et al., 1985).

7. Summary

Buprenorphine is an effective, safe medication for use in the treatment of opioid dependence. It has a unique pharmacologic profile, and understanding its pharmacologic effects helps in understanding and guiding its clinical use. Like other medications for medical disorders, its optimal use will depend upon appropriate and
adequate dosing and the concurrent delivery of non-medication services that directly and indirectly address the underlying disorder (opioid dependence). However, because of its safety (secondary to its partial agonist character), low abuse potential (e.g. naloxone-related precipitated withdrawal if the buprenorphine/naloxone tablet is injected by an opioid-dependent person), and clinical flexibility in use (e.g. daily vs. thrice-weekly dosing vs. take-homes), the availability of buprenorphine and buprenorphine combined with naloxone are valuable additions to the formulary of medications for treating opioid dependence (Raisch et al., 2002). The pharmacologic profile of buprenorphine suggests it may be ideally suited for use in non-traditional treatment settings, such as office-based practices and other clinics outside the traditional opioid treatment delivery system.

Acknowledgements

This work was supported by USPHS grants R01-DA12220 and P50-DA 05273 (Rolley E. Johnson), K02-DA00332 and R01-DA08045 (Eric C. Strain), and R01-DA11160 and R01-DA13638 (Leslie Amass) from the National Institute on Drug Abuse.

References


Doxey, J.C., E...


comparison of buprenorphine and methadone. Pharmacopsychia-
try 35, 159–164.
Seow, S.W., Quigley, A.J., Ilett, K.F., Dusci, L.J., Swensen, G.,
buprenorphine/naloxone in opioid-dependent humans. Psycho-
and withdrawal. In: Strain, E.C., Stitzer, M.L. (Eds.), Methadone
Treatment for Opioid Dependence. The Johns Hopkins University
effects of buprenorphine, hydromorphone and naloxone in metha-
993.
rison of buprenorphine and methadone in the treatment of
norphine effects in methadone-maintained volunteers: effects at 2 h
1997. The effects of buprenorphine in buprenorphine-maintained
buprenorphine versus buprenorphine/naloxone tablets in non-
Strain, E.C., Moody, D.E., Stoller, K., Walsh, S.L., Bigelow, G.E.,
2002a. Bioavailability of buprenorphine solution versus tablets
during chronic dosing in opioid-dependent subjects. Drug Alcohol
Depend. 66 (Suppl. 1), S176.
Strain, E.C., Walsh, S.L., Bigelow, G.E., 2002b. Blockade of hydro-
morphine effects by buprenorphine/naloxone and buprenorphine.
Psychopharmacology 159, 161–166.
Med. J. 302, 969.
Summerfield, R.J., Allen, M.C., Moor, R.A., Sear, J.W., McQuay,
40, 914.
The Manif-2000 Study Group, Carrieri, M.P., Vlahov, D., Dellen-
monica, P., Gallais, H., Lepeu, G., Spire, B., Obadia, Y., 2000. Use of
buprenorphine in HIV-infected injection drug users: negligible
impact on virologic response to HAART. Drug Alcohol Depend.
60, 51–54.
The Manif 2000 Study Group, Moatti, J.P., Carrieri, M.P., Spire, B.,
HAART in French HIV-infected injecting drug users: contribution
of buprenorphine drug maintenance treatment. AIDS 14,
151–155.
Thirion, X., Micaleff, J., Barrau, K., Djezzar, S., Lambert, H.,
Sanmarco, J.L., Lagier, G., 2001. Recent evolution in opiate
dependence in France during generalization of maintenance treat-
Thirion, X., Lapierre, V., Micaleff, J., Ronfle, E., Masut, A., Pradel,
V., Coudert, C., Mabriez, J.C., Sanmarco, J.L., 2002. Buprenor-
phine prescription by general practitioners in a French region.
Drug Alcohol Depend. 65, 197–204.
depression caused by sublingual buprenorphine. Lancet 23, 179–
180.
Toxicol. 22, 430–434.
Traquci, A., Tournoud, C., Flesch, F., Kopferschmitt, J., Kintz, P.,
Deveaux, M., Ghysel, M.H., Marquet, P., Pepin, G., Petit, G.,
users on substitution therapy: 29 non-fatal and 20 fatal cases. La
Presse Médicale 27, 557–561.
Uehlinger, C., Déglon, J.-J., Livoti, S., Petitjean, S., Waldvogel, D.,
Ladewig, D., 1998. Comparison of buprenorphine and metha-
done in the treatment of opioid dependence. Eur. Addict. Res. 4,
13–18.
Vallner, J.J., Stewart, J.T., Kotzan, J.A., Kirsten, E.B., Honigberg,
J.L., 1981. Pharmacokinetics and bioavailability of hydromor-
phone following intravenous and oral administration in human
Vignau, J., 1998. Preliminary assessment of a 10-day rapid detoxifica-
Vignau, J., Duhamel, A., Catteau, J., Legal, G., Pho, A.H., Graillies,
Practice-based buprenorphine maintenance treatment (BMT):
how do French healthcare providers manage the opiate-addicted
patients? J. Subst. Abuse Treat. 21, 135–144.
Walsh, S.L., Preston, K.L., Stitzer, M.L., Cone, E.J., Bigelow, G.E.,
1994. Clinical pharmacology of buprenorphine: ceiling effects at
Walsh, S.L., June, H.L., Schuh, K.J., Preston, K.L., Bigelow, G.E.,
Stitzer, M.L., 1995a. Effects of buprenorphine and methadone in
methadone-maintained subjects. Psychopharmacology 119, 268–
276.
administration of buprenorphine in humans: partial agonist and
Walsh, S.L., Eisenberg, T., 2003. Clinical pharmacology of bupre-
norphine: extrapolating from the laboratory to the clinic. Drug
Alcohol Depend. 70, Suppl. 1, S13–S27.
Walter, D.S., Inturrisi, C.E., 1995. Absorption, distribution, metabo-
lism, and excretion of buprenorphine in animals and humans. In:
Cowan, A., Lewis, J.W. (Eds.), Buprenorphine: Combating Drug
Welsh, C.J., Suman, M., Cohen, A., Broyles, L., Bennett, M.,
Weintraub, E., 2002. The use of intravenous buprenorphine for
the treatment of opioid withdrawal in medically ill hospitalized
patients. Am. J. Addict. 11, 135–140.
Weinberg, D.S., Inturrisi, C.E., Reidenberg, B., Moulin, D.E., Nip,
absorption of selected opiate analgesics. Clin. Pharmacol. Ther. 44,
335–342.
White, R., Alcorn, R., Feinmann, C., 2001. Two methods of
community detoxification from opiates: an open-label comparison
of lofexidine and buprenorphine. Drug Alcohol Depend. 65, 77–
83.
Zacny, J.P., Conley, K., Galinkin, J., 1997. Comparing the subjective,
psychomotor and physiological effects of intravenous buprenor-
Ther. 282, 1187–1197.
Zhi-Min, L., Zhi-Ji, C., Xiao-Ping, W., Yun, G.E., Chun-Mei, L.I.,
1997. Rapid detoxification of heroin dependence by buprenor-