Buprenorphine in the treatment of opioid dependence

Methadone has been the mainstay of pharmacological management of opioid dependence since the 1960s but buprenorphine is fast gaining acceptance among addiction specialists and patients. This article provides an overview of buprenorphine, its pharmacology, clinical efficacy and role in the treatment of opioid dependence.

Opioid dependence (heroin being the most commonly misused opioid) is often a chronic, relapsing condition with wide-ranging negative consequences to the addict, his/her family and society. Estimates indicate that there are around 160 000 heroin addicts in treatment in the UK (National Treatment Agency for Substance Misuse, 2005) and it is argued that there are two to three times this number who are not engaged with treatment services. Heroin addicts have high rates of physical illness (especially bloodborne viral infections), a 12-fold increased risk of mortality (Oppenheimer et al, 1994), excess psychiatric morbidity, grossly impaired family, social and occupational functioning, and they cost the UK criminal justice system in excess of £2 billion per annum.

Over the last four decades (1960s to late 1990s), methadone has been the mainstay of pharmacological treatment for opioid dependence. Buprenorphine was licensed for opioid substitution treatment in the UK in 1998 and is fast gaining acceptance among patients and addiction specialists (Luty et al, 2005). An audit of the prescribing patterns in drug misuse services in the UK found that 26% of all patients prescribed opioid substitutes received a buprenorphine prescription (National Treatment Agency for Substance Misuse, 2007). In the UK, buprenorphine is a Class C, Schedule III controlled drug under the Misuse of Drugs Act 1971.

Many physicians will be familiar with buprenorphine (trade name Temegesic, Schering-Plough, Welwyn Garden City), as it has been used since the 1980s as an analgesic for management of moderate to severe pain. This article introduces buprenorphine (in the treatment of opioid dependence) to the non-specialist and provides a brief overview of its pharmacological profile, clinical efficacy and its advantages over methadone.

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Pharmacological profile

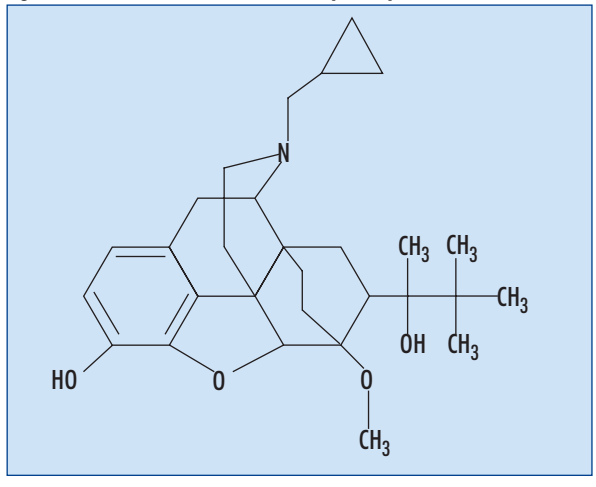
Mode of action

Buprenorphine (marketed in the UK as Subutex, Schering-Plough, Welwyn Garden City) is available in 0.4 mg, 2 mg and 8 mg tablets for sublingual administration. Buprenorphine is a derivative of the morphine alkaloid thebaine (*Figure 1*) and is a mixed agonist-antagonist at opioid receptors: a partial agonist at the μ opioid receptor, with low intrinsic activity and high affinity, and an antagonist at the κ opioid receptor. This unique receptor binding profile is clinically important for two reasons. First, because of its partial agonistic activity (and low intrinsic activity), it only partially activates μ receptors and so it is less euphoric, less sedating and less likely to cause respiratory depression than full agonists such as heroin and methadone (*Figure 2*). Second, its high affinity for μ receptors means that it prevents other opioids from occupying these receptors and so reduces the impact of heroin or other opioids if taken in addition to buprenorphine. Buprenorphine's μ and κ receptor activity also explains its bell-shaped dose–response curve (Johnson et al, 2003).

Pharmacokinetics

Buprenorphine undergoes extensive first-pass metabolism if administered orally, but has a bioavailability of 31% if taken sublingually. It is extensively protein bound (96%) (Walter and Inturrisi, 1995) and has a plasma

Figure 1. The molecular structure of buprenorphine – C29H41NO4.



elimination half-life of 37 hours. This long elimination half-life combined with its high lipophilicity makes once daily dosing (and even alternate day dosing) appropriate (Eissenberg et al, 1997; Perez de los Cobos et al, 2000). Buprenorphine undergoes hepatic biotransformation via two pathways: N-dealkylation (CYP3A4 isoenzyme) and glucoronide conjugation. Excretion is mostly in faeces and urine. Cytochrome P3A4 isoenzyme inhibitors such as erythromycin, imipramine and protease inhibitors for the treatment of human immunodeficiency virus (HIV) can lead to increases in buprenorphine levels and enzyme inducers such as alcohol and antiepileptics can lower buprenorphine levels, and so the dose should be adjusted accordingly.

Safety and tolerability

Buprenorphine is a relatively safe drug. Because of its 'ceiling effect' (as it is only a partial agonist) it is less likely to cause respiratory depression and hence is safer in overdose than heroin and methadone (Auriacombe, 2001). However, when taken with other CNS depressants like alcohol and benzodiazepines, buprenorphine can be fatal (Kintz, 2002). Although buprenorphine has not been shown to have any specific teratogenic potential, its use in pregnancy and breast feeding is not yet recommended, although it is a potentially useful treatment option in this group (Dunlop et al, 2003).

The side-effect profile of buprenorphine is similar to other opioids and includes headaches, nausea, sweating and constipation. In most cases such side effects are only fleeting and rarely require drug discontinuation. Hypersensitivity reactions are very rare. Buprenorphine can occasionally result in elevated levels of liver enzymes (aspartate aminotransaminase and alanine aminotransaminase) and isolated cases of hepatitis following injection of crushed buprenorphine tablets have been reported (Berson et al, 2001). Hence it is good practice to assess liver function before treatment initiation and then to periodically monitor liver function during treatment (Johnson et al, 2003).

Efficacy

Buprenorphine in opioid maintenance treatment

A typical recommended starting dose is between 4 and 8 mg per day. To avoid precipitating symptoms of opioid withdrawal administer the first dose of buprenorphine only when craving and withdrawal symptoms begin to emerge. This is typically seen 8–12 hours after the last use of heroin or 24–36 hours after the last dose of methadone. The dose should then be increased by 2–4 mg per day until withdrawal symptoms are controlled for a 24-hour period. Patients used to the mild sedative effect of methadone may need regular reassurance for the first few days and regular patient reviews can help to monitor withdrawal symptoms and craving, and thereby determine the appropriate dose of buprenorphine required for maintenance – usually 12–16 mg per day (Lintzeris et al, 2006). Very low doses (<4 mg/day) are ineffective in reducing heroin use and result in treatment drop out.

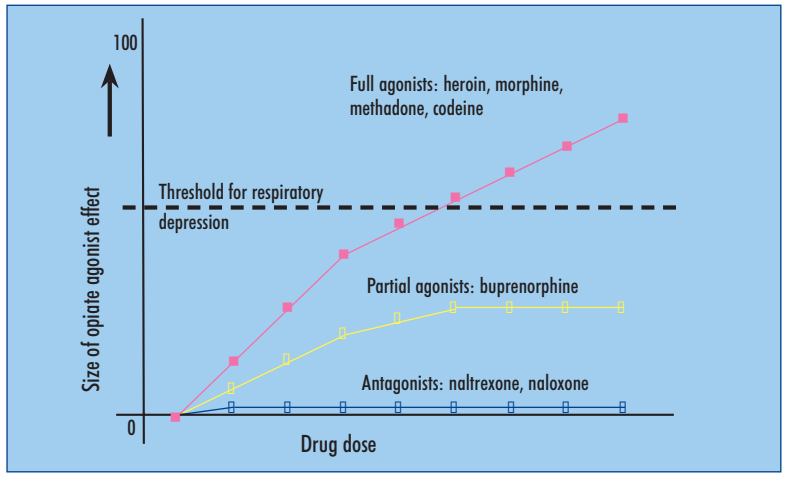


Figure 2. Comparative agonist effects of various opioids. From Law et al (2004).

Maintenance buprenorphine prescribing has also been found to be feasible and effective in primary care in the UK (Royal College of General Practitioners, 2004). When the decision is taken to stop buprenorphine, a gradual reduction is recommended (*Table 1*), unless a quicker detoxification is indicated.

An unpublished review from 2005, that compared 'buprenorphine maintenance with placebo or methadone maintenance for opioid dependence' using retention in treatment and use of heroin 'on top' as the key measures of effectiveness, concluded that:

- Buprenorphine is more effective than placebo as a maintenance treatment
- Low-dose buprenorphine (<6 mg) is as effective as low-dose methadone (<40 mg)
- Medium-dose buprenorphine (6–12 mg) is comparable to medium-dose methadone (40–65 mg)
- Medium-dose buprenorphine is less effective than high-dose methadone (>80 mg), albeit with no studies comparing high-dose methadone with high-dose buprenorphine.

Although this review is unpublished, the information it contains is available in Connock et al (2007). Overall, this review and most of the other efficacy research (Ling et al, 1998; Ahmadi, 2002) for buprenorphine maintenance treatment concludes that buprenorphine is a feasible and effective treatment for opioid maintenance.

Table 1. Cessation of buprenorphine maintenance treatment

Dose of buprenorphine	Reduction rate
More than 16 mg	4 mg per week or fortnightly
8–12 mg	2–4 mg per week or fortnightly
Less than 8 mg	<2 mg per week or fortnightly

From Lintzeris et al (2006)

Buprenorphine for opioid detoxification

Detoxification is the process of achieving a drug-free state, usually within 7–14 days. Buprenorphine may be used on its own or along with other symptomatic treatments such as non-steroidal anti-inflammatory drugs, anxiolytics and hypnotics, antiemetics and antidiarrhoeals. *Table 2* gives suggestions for detoxification regimens.

A Cochrane review (Gowing et al, 2006) evaluated the effectiveness of buprenorphine for the management of opioid withdrawal. Buprenorphine was noted to be more effective than clonidine and/or benzodiazepines for opioid detoxification on outcome measures such as retention in treatment, severity of withdrawals and completion of treatment. Available evidence also suggests that buprenorphine is as effective as methadone in opioid detoxification (Lintzeris et al, 2002), but results in lower withdrawal symptom severity and a shorter duration of withdrawal symptoms.

Buprenorphine *vs* methadone

Table 3 gives a comparison of buprenorphine and methadone.

Table 2. Suggested detoxification regimens for patients using heroin

Low-dose user	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10
	4 mg	6 mg	8 mg	10 mg	8 mg	6 mg	4 mg	2 mg	0.8 mg	0.4 mg
High-dose user	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10
	4 mg	8 mg	12 mg	16 mg	12 mg	8 mg	4 mg	2 mg	0.8 mg	0.4 mg

Table 3. A comparison of methadone and buprenorphine

	Buprenorphine	Methadone
Receptor binding	Partial μ agonist κ antagonist	Full μ agonist Nil antagonist action
Oral absorption	Poor	Good
Route of administration	Sublingual	Oral
Time to peak plasma concentration	90–150 minutes	2–6 hours
Elimination half-life	5 hours	15–22 hours
Euphoric and sedating effects	Less	More
Side-effect profile	Similar to other opioids	Similar to other opioids
Equivalent doses	12–16 mg	50–80 mg
Overdose risk	Low	High
Use in pregnancy	Not recommended	Can be used
Withdrawal symptoms on discontinuation	Less severe	More severe
Initiation onto naltrexone	Within 5–7 days	Within 7–10 days
Cost (8 mg tablet *vs* 30 mg liquid)	£2.80	£0.44

When do you prefer buprenorphine to methadone?

Buprenorphine may be preferred to methadone in:

- Patients who have intolerable side effects to methadone or those who do not want methadone
- Patients who are at high risk of overdose
- Patients who want short-term (weeks or months) opioid stabilization before detoxification
- Patients on concurrent medication – buprenorphine is less affected by enzyme inducers and inhibitors than methadone
- Patients who are hoping to start naltrexone soon after detoxification
- Patients who prefer the less sedating, 'clear headed' effects of buprenorphine to methadone
- Patients who have failed a previous trial of methadone.

Buprenorphine: the future

The only preparation of buprenorphine currently licensed in the UK for treatment of opioid addiction is the tablet for sublingual administration. However, there have been reports of the tablet being dissolved and injected intravenously (Obadia et al, 2001). In view of this abuse potential, a combination tablet of buprenorphine and naloxone, in a 4:1 ratio (Mendelson and Jones, 2003), has recently been licensed for use in the USA and Europe. When this tablet is taken sublingually naloxone is inactive, but if it is injected, naloxone becomes active and induces a distressing withdrawal, thus putting people off attempting intravenous misuse (Stoller et al, 2001). Preliminary investigations are underway of the feasibility and efficacy of injectable depot formulations of buprenorphine that offer advantages including better patient compliance, higher bioavailability, once-monthly administration and sustained release (Sigmon et al, 2006). BJHM

The authors would like to thank Dr Fergus Law for his permission to reproduce Table 2.

Conflict of interest: none.

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KEY POINTS

- Buprenorphine is a partial agonist at μ opioid receptors possessing high affinity and low intrinsic activity at these receptors.
- It is less sedating, less euphoric and is safer in overdose than methadone.
- Buprenorphine is an effective alternative to methadone for detoxification and maintenance treatment in opioid dependence.
- Trials are underway evaluating the feasibility of injectable depot formulations of buprenorphine.