

1 Clinical Pharmacology

1.1 General Information

What is Buprenorphine?

Buprenorphine is a derivative of the morphine alkaloid, thebaine, and is a *partial opioid agonist* at the mu (μ) opioid receptors in the nervous system. Although buprenorphine is a potent μ -receptor agonist at low doses, there is a “ceiling” on its maximal opioid activity (Walsh *et al* 1994; Walsh *et al* 1995). Buprenorphine diminishes cravings for heroin, and prevents or alleviates opioid withdrawal in dependent heroin users. Buprenorphine has a higher affinity for μ opioid receptors than full opioid agonists. Because of this, buprenorphine can block the effects of other opioid agonists in a dose-dependent fashion. By its dual effects of reducing craving and attenuating the response to administered heroin, buprenorphine reduces the self-administration of heroin. Methadone, a full opioid agonist, also reduces the impact of additional heroin, but the effect of methadone is primarily due to the induction of cross-tolerance which is dose dependent. In contrast buprenorphine achieves its effect primarily by prolonged occupancy of a high proportion of opioid receptors, blocking the action of heroin.

Unlike methadone, the effect of buprenorphine on respiratory depression reaches a ceiling, with higher doses not increasing respiratory depression to a significant degree. However, if buprenorphine is used in combination with other central nervous system depressants, such as benzodiazepines, the combined effect on respiration can be life threatening.

Buprenorphine also exhibits antagonist effects at the kappa (κ) opioid receptor. The role of these receptors in humans is still poorly understood.

What form does it come in?

Two buprenorphine products are currently registered in Australia for the treatment of opiate dependence within a framework of medical, social and psychological treatment: the mono product (Subutex®) is a sublingual tablet containing buprenorphine hydrochloride in 0.4, 2, and 8mg strengths; the combination product (Suboxone®) is a sublingual tablet containing buprenorphine hydrochloride and naloxone hydrochloride in a ratio of 4:1. Suboxone® is available in two dosage strengths: 2mg buprenorphine and 0.5mg naloxone, and 8mg buprenorphine and 2mg naloxone. Buprenorphine is also registered in Australia as Temgesic® sublingual tablets and ampoules for intramuscular or subcutaneous injection, for short-term (not more than one week) relief of moderate to severe pain, including post-operative and terminal and chronic pain. A low dose buprenorphine patch for transdermal administration is now available in Australia for pain relief.

Sublingual buprenorphine tablets have approximately 30–35% of the bioavailability of intravenous buprenorphine preparations¹. The bioavailability of sublingual buprenorphine is largely dependent on the time the drug is in contact with the oral mucosa and appears to improve as individuals practice taking their medication.

How is it metabolised?

Peak plasma concentrations are achieved one to two hours after sublingual administration. Buprenorphine undergoes extensive first pass metabolism when taken orally. The major metabolite, norbuprenorphine, has some opioid activity but the extent of its contribution to the effects of buprenorphine is unknown.

Buprenorphine is principally metabolised by two hepatic pathways: conjugation with glucuronic acid and *N*-dealkylation, mediated by the cytochrome P450 3A4 isozyme. The metabolites are excreted in the biliary system, with enterohepatic cycling of buprenorphine and its metabolites. Most of the drug is excreted in the faeces and, to a lesser extent, in the urine.

Duration of action

Buprenorphine is a long-acting drug with a terminal elimination half-life of 24 to 37 hours. Peak clinical effects occur one to four hours after sublingual administration. Typically effects will continue to be experienced for up to 12 hours at low doses (2 mg), but as long as 48 to 72 hours at higher doses (16 or 32 mg). The prolonged duration of effect at high doses enables alternate-day, and even 3-days-a-week dispensing regimes.

Table 1: Onset and duration of response to buprenorphine

Onset of effects	30–60 minutes
Peak clinical effects	1–4 hours
Duration of effects	8–12 hours at low dose (e.g. 2 mg)
	24–72 hours at high dose (e.g. >16 mg)

1.2 Withdrawal syndrome following buprenorphine maintenance treatment

The partial agonist properties of buprenorphine, along with its slow dissociation from opioid receptors result in a withdrawal syndrome that is delayed and may be milder than withdrawal from heroin, morphine and methadone (Cami *et al* 1991; Horgan 1989; Jasinski 1981; Jasinski *et al* 1982; Mello & Mendelson 1980; Mudric *et al* 1998; Sam *et al* 1991; San *et al* 1992). Research evidence regarding the nature and severity of withdrawal following cessation of buprenorphine maintenance treatment remains limited.

¹ The majority of early studies of sublingual buprenorphine used a liquid solution of buprenorphine in 30% aqueous ethanol, with a bioavailability of approximately 40% of intravenous preparations. Studies comparing the bioavailability of tablet and solution formulations for sublingual administration have found considerable between-subject variability, and differences for chronic compared to acute dosing (Chiang & Hawks 2003; Strain *et al* 2004). When administered for periods greater than 14 days, the bioavailability of the tablet formulation is around 70% that of solution formulation (Strain *et al* 2004).

Furthermore, many of the early studies of buprenorphine withdrawal relied on observers' assessments of objective withdrawal signs, which can produce a significantly different view to subjective assessments by patients of withdrawal severity (Kosten *et al* 1985). Typically, the withdrawal syndrome following the abrupt cessation of long-term buprenorphine treatment emerges within three to five days of the last dose, and mild withdrawal features continue for up to several weeks.

1.3 Safety and side effects

High doses: Dose response studies show that high doses of buprenorphine (16mg daily or more) do not result in substantially greater peak opioid effects than lower doses (8 or 12mg) (Walsh *et al* 1995). Doses many times greater than normal therapeutic doses appear to be well-tolerated in most individuals, and rarely result in clinically-significant respiratory depression, except in individuals who are not opioid-tolerant. However, even low doses of buprenorphine can be toxic when combined with sedatives such as benzodiazepines and alcohol (Faroqui *et al* 1983; Forrest 1983; Papworth 1983; Sekar & Mimpriss 1987).

Buprenorphine is safer in high doses than full opioid agonists

Combined with other drugs: The safety of buprenorphine mixed with high doses of other sedative drugs, such as alcohol or benzodiazepines and antipsychotics, is still unclear, with deaths having been reported (Brenet *et al* 1998; Gaulier *et al* 2000; Reynaud *et al* 1997; Reynaud *et al* 1998). Naloxone may be of limited use in resuscitating individuals who have overdosed on high doses of buprenorphine (See section 5.2 on Overdose). For the majority of fatalities reported to date involving buprenorphine and benzodiazepines, patients were injecting buprenorphine along with benzodiazepines or taking large amounts of buprenorphine outside of a doctor's care. Legitimate and appropriate prescription of these therapeutics coupled with responsible use by patients is unlikely to lead to adverse consequences.

Precaution should be exercised when buprenorphine is administered concomitantly with CYP3A4 inhibitors (e.g. protease inhibitors, some drugs in the class of azole antimycotics such as ketoconazole, calcium channel antagonists such as nifedipine, and macrolide antibiotics, such as erythromycin and clarithromycin) as this may lead to increased plasma concentrations of buprenorphine. (See Appendix 1)

Buprenorphine is not safe when mixed with high doses of other sedatives

Side effects: The side effects of buprenorphine are similar to those of other opioids (Lofwall *et al* 2005), the most common being:

- constipation
- disturbed sleep
- drowsiness
- sweating
- headaches
- nausea
- reduced libido.

Many patients report less sedation on buprenorphine than on methadone. Research evidence suggests that buprenorphine has minimal effect on psychomotor performance (Lenne *et al* 2003; Mintzer *et al* 2004), and less effect than methadone (Soyka *et al* 2005) or slow release oral morphine (Giacomuzzi *et al* 2005). Any effect is likely to be greatest during the early stages of treatment or following dose increases. At such times patients should be advised to exercise caution in driving or operating machinery.

Buprenorphine appears to have minimal impact on hepatic function, although there have been some reports of acute hepatitis following very high doses (>32mg iv).

Side effects of buprenorphine are similar to other opioids

Under certain circumstances, buprenorphine may precipitate opioid withdrawal symptoms one to four hours after the first dose. It has a higher affinity and lower intrinsic activity than full agonists such as methadone, morphine or heroin. Consequently, buprenorphine displaces agonists from opioid receptors and, in the short term, may not produce sufficient agonist effects to compensate for the displaced methadone or heroin, producing opioid withdrawal as the buprenorphine reaches its peak effects (approx. one to four hours after initial administration). The phenomenon of precipitated withdrawal has particular clinical relevance during the induction of heroin users and methadone patients. It can largely be avoided by using appropriate dose induction procedures (see Section 3.3).

1.4 Drug Interactions

The principal drug interactions of buprenorphine relate to its opioid activity.

- **Other sedatives:** Buprenorphine exerts additive sedative effects when used in conjunction with other sedating medications. These include other opioids, benzodiazepines, alcohol, tricyclic antidepressants, sedating anti-histamines, and major tranquillisers. **The combination of buprenorphine with benzodiazepines, alcohol and other sedatives has been associated with fatal overdoses.**
- **Opioid antagonists (naloxone and naltrexone):** Buprenorphine has affinity for μ opioid receptors similar to the opioid antagonists. In the event of overdose of buprenorphine, very high doses of naloxone may be required to partially reverse its effects. Cases have been reported in which naloxone in doses of 10 to 35mg was required, while in other cases doses of 2mg or less were reported to be effective in reducing respiratory depression (Boyd *et al* 2003). Because of the uncertain response to naloxone, prolonged ventilatory support may be required in overdoses involving buprenorphine. Naltrexone can precipitate a withdrawal reaction in patients on buprenorphine, although the effect may be delayed (2 to 4 hours, occasionally up to 8 hours).
- **Opioid agonists:** Buprenorphine exerts a degree of blockade to the effects of full agonist opioids, which may complicate the use of additional opioids for analgesia (see section 5.7). The initial dose of buprenorphine can precipitate opioid withdrawal in patients who have recently used an opioid drug.
- **Hepatic enzyme inducers and inhibitors:** Buprenorphine metabolism can be influenced by the presence of drugs and other compounds that are also metabolised by or affect the activity of the cytochrome system (see Appendix 1). Patients who are concurrently prescribed or using inhibitors of cytochrome P450 3A4 may have increased buprenorphine blood concentrations, and those taking inducers may have decreased blood concentrations. Such interactions are probably seldom of clinical significance.

1.5 Buprenorphine–naloxone combination product (Suboxone®)

The buprenorphine–naloxone combination product was developed to limit the abuse potential of buprenorphine by reducing the potential for injection, especially by opioid dependent users who are not in treatment. At this time there is little evidence to determine the extent to which this will be achieved, although there have been few reports of significant abuse or diversion of Suboxone® in the three years since it was adopted for clinical use in the USA (Stanton *et al* 2005).

The different sublingual and parenteral potency profiles of buprenorphine and naloxone is the rationale for the combination product. When buprenorphine is used sublingually, bioavailability is somewhere between 30 and 55% while the bioavailability of naloxone via this route is less than 10%. Consequently, when Suboxone® is taken sublingually, it will act as if it was buprenorphine alone, with no apparent effect from the naloxone. Addition of naloxone does not reduce bioavailability of buprenorphine (Chiang & Hawks 2003). In fact there is some evidence that the bioavailability of chronically administered buprenorphine–naloxone may be higher than buprenorphine alone (Strain *et al* 2004). However, if the combined preparation is injected, the naloxone will have a substantial effect and is likely to attenuate the effects of the buprenorphine in the short-term and is also likely to precipitate withdrawal in opioid-dependent individuals on full opioid agonists (Stoller *et al* 2001).

TABLE 2: EFFECTS OF MONO (SUBUTEX®) AND COMBINATION (SUBOXONE®) PREPARATIONS OF BUPRENORPHINE IN VARIOUS SITUATIONS

Note: Research and clinical experience in different populations of opioid users of the effects of buprenorphine, alone and in combination with naloxone, are limited. This table summarises current expert opinion of the likely immediate effects of buprenorphine, in doses of 8 to 32mg, in different situations.

Population	Combination product (Suboxone®)		Mono product (Subutex®)
	Sublingual (poor bioavailability of naloxone)	i.v. (high bioavailability of naloxone)	Sublingual or i.v.
Dependent heroin user Heroin 1 hr ago	Withdrawal precipitated by buprenorphine	Severe withdrawal due to naloxone and buprenorphine	Precipitate withdrawal
Heroin >12 hrs ago	Agonist effects	May be mild withdrawal	Agonist effects
Non-dependent heroin user	Agonist effects	Attenuated agonist effect	Agonist effects
Opiate—naïve	Agonist effects (reduced if swallowed)	Agonist effect initially attenuated	Agonist effects (reduced effects if swallowed)
Subutex maintenance	Agonist effect	Agonist effect may initially be attenuated	Agonist effects
Methadone maintenance (dose <24 hrs ago)	Precipitated withdrawal	Severe withdrawal due to naloxone and buprenorphine	Precipitated withdrawal

All opioids have abuse potential, but as indicated in the table above, people who are frequent users of heroin, methadone, or other opioid agonists that bind less tightly to opioid receptors than buprenorphine, are unlikely to abuse buprenorphine. The effect of buprenorphine (taken sublingually or by intravenous injection) in people in naltrexone maintenance treatment remains unclear. Administration of buprenorphine to this population may result in an attenuated agonist effect, particularly with low doses of naltrexone, as is generally the case with implanted preparations of naltrexone.

As with all opioid drugs, the prescription of the buprenorphine–naloxone combination as a takeaway medication for unsupervised administration needs to be based on a careful assessment of the risk of injection of the preparation by the person for whom it was intended as well as the potential for diversion for unauthorised use.

From Table 2 it will be apparent that the group most likely to inject the buprenorphine–naloxone combination product will be people on buprenorphine maintenance programs. In particular, there is a risk that people prescribed unsupervised doses of the combination product may inject their own medication. Injection of drugs designed for sublingual administration is a health risk, and doctors have an obligation to monitor patients closely. Specifically, patients receiving doses for unsupervised administration should be monitored for signs of fresh injecting sites, and takeaway doses should not be supplied to people with evidence of continued, recent injecting. (See also section 3.6.)

TABLE 3 SUMMARY OF PHARMACOLOGICAL AND CLINICAL PROPERTIES OF BUPRENORPHINE

Property	Clinical implication
Produces opioid effects	Reduces cravings for heroin and enhances treatment retention.
Prevents or alleviates heroin withdrawal symptoms	Can be used for maintenance or withdrawal treatment.
Diminishes the effects of additional opioid use (e.g. heroin)	Diminishes psychological reinforcement of continued heroin use. May complicate attempts at analgesia with opioid agonists (e.g. morphine).
Long duration of action	Allows for once-a-day to three-times-a-week dosing.
Ceiling on dose response effect	Less sedating than full agonists (heroin, morphine or methadone). Buprenorphine doses above 12mg/day may not increase the opioid agonist effects, but will prolong the duration of action. Safer in overdose, as high doses in isolation rarely result in fatal respiratory depression.
Sublingual preparation	Safer in accidental overdose (e.g. in children) as poorly absorbed orally. More time involved in supervised dispensing.
Modified withdrawal precipitated by opioid antagonists.	Treatment with naltrexone can be commenced within 5–7 days of buprenorphine. May complicate management of opioid overdose requiring high naloxone doses.
Side effect profile similar to other opioids	Generally well tolerated, with most side effects transient.