Australian Government

National clinical guidelines and procedures for the use of buprenorphine in the maintenance treatment of opioid dependence

National Drug Strategy

National clinical guidelines and procedures for the use of buprenorphine in the treatment of opioid dependence

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National Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opoid Dependence

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Table of Contents

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This revision of the guidelines and the original guidelines were developed through a consensus process by a working party of senior Australian clinicians and researchers from several jurisdictions who have experience in the use of buprenorphine. The revisions to the guidelines are based on research evidence and clinical experience with buprenorphine since publication of the first national guidelines.

The first national guidelines in turn were based on work undertaken by Turning Point Alcohol and Drug Centre for trials of buprenorphine treatment. The authors wish to acknowledge the many people who have contributed to the guidelines as they have developed. In particular, the following people have contributed to this version of the guidelines:

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Introduction

Buprenorphine is registered in Australia for the management of opioid dependence within a framework of medical, social and psychological treatment. Buprenorphine is indicated for use in detoxification and maintenance treatment of opioid dependence. To assist in the safe and effective provision of buprenorphine treatment in Australia, these national guidelines were commissioned by the Commonwealth Department of Health and Ageing under the auspices of the National Expert Advisory Committee on Illicit Drugs (NEACID).

Until recently the only buprenorphine preparation available in Australia for the treatment of opioid dependence was Subutex®, a sublingual tablet containing only buprenorphine (the mono product). A second sublingual tablet preparation, Suboxone®, containing buprenorphine and naloxone (the combination product) was approved by the Therapeutic Goods Administration on 27 July 2005. This revision of the guidelines considers both buprenorphine preparations. The general chemical name "buprenorphine" is used for information that applies to either preparation. Where it is necessary to distinguish between the preparations, the term "mono product" is used for Subutex® and "combination product" is used for Suboxone.

The guidelines have also been updated to reflect changes in research and clinical knowledge of buprenorphine.

There is limited experience with the combination product (Suboxone®), and following its release,a post-marketing surveillance study will be undertaken by the National Drug and Alcohol Research Centre. This study will assess relative rates of diversion of the mono and combination products, as well as the relative efficacy of these tablets in the usual practice setting. This study is expected to further inform practice in Australia.

Section 1 reviews the clinical pharmacology of the preparations; Section 2 covers the commencement of buprenorphine for either maintenance or withdrawal treatment; Section 3 provides guidance on the use of buprenorphine in maintenance treatment of opioid dependence; Section 4 provides guidance on the use of buprenorphine in the management of opioid withdrawal; Section 5 covers complications and adverse events; and Section 6 discusses prescribing and dispensing issues.

The guidelines have been endorsed by the Royal Australian College of General Practitioners, the Royal Australasian College of Physicians and the Australasian Professional Society on Alcohol and other Drugs.

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 preparations[1]. 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.

	Combination product (Suboxone®)		Mono product (Subutex®)
Population	**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 buprenorhine 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.

2 Entry into buprenorphine treatment

2.1 Suitability for treatment with buprenorphine

There is no good evidence indicating who is better suited to methadone or buprenorphine maintenance treatment or detoxification.

The following guidelines should be taken into account when considering a person's suitability for treatment with buprenorphine for either maintenance or withdrawal.

2.1.1 Indications

(1) Buprenorphine treatment is only indicated for those who are opioid-dependent (see box at right).

Note: Neuroadaptation is not a prerequisite for the diagnosis of drug-dependence. However, in the absence of neuroadaptation, the prescribing medical practitioner must clearly demonstrate potential benefits to the individual's health and well-being that outweigh the potential disadvantages of buprenorphine treatment, and alternative treatment options should be carefully considered.

Evidence of neuroadaptation (or physical dependence) is indicated by:

- tolerance to the opioid;
- onset of withdrawal syndrome on stopping or decreasing use.

Diagnostic Definition of Opioid Dependence (DSM IV)

'A maladaptive pattern of substance use leading to clinically significant impairment or distress as manifested by three or more of the following, occurring at any time in the same 12 month period.'

- *Tolerance* as defined by either of the following:
  - A need for markedly increased amounts of opioids to achieve intoxication or desired effect;
  - Markedly diminished effect with continued use of the same amount of opioids.
- *Withdrawal* as manifested by either of the following:
  - The characteristic withdrawal syndrome for opioids;
  - Opioids, or a closely related substance, being taken to relieve or avoid withdrawal symptoms.
- *Impaired control over use*: Opioids often taken in larger amounts or over longer period than intended.
- *Wish to quit:* A persistent desire or unsuccessful attempts to cut down or control opioid use.
- *Time factor:* A great deal of time regularly spent in activities necessary to obtain opioids, use opioids, or recover from their effects.
- *Life-style changes:* Important social, occupational, or recreational activities given up or reduced because of opioid use.
- *Continued use despite awareness it is causing harm:* The opioid use continued, despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by opioids.

(2) The patient must be at least 16 years of age.

Buprenorphine has been registered for administration to people aged 16 and over. Nonetheless caution should be exercised in prescribing a drug of dependence for anyone in the 16–17 age group and a second or specialist opinion should be sought before treating anyone under 18 years of age. However, positive results have been reported from the combination of buprenorphine with behavioural interventions for the treatment of opioid-dependent adolescents (Marsch *et al* 2005).

(3) It is good practice to ensure that the patient can provide proof of identity — check the requirements in your jurisdiction regarding treatment with an S8 medication (see Appendix 2 for useful contacts).

(4) The patient must be capable of giving informed consent to treatment with buprenorphine.

Suitability for Buprenorphine Treatment

opioid-dependent

16 years or older

proof of identity

capable of informed consent

2.1.2 Contraindications

(1) Anyone with known hypersensitivity and/or severe side-effects from previous exposure to buprenorphine or the combination product is ineligible for buprenorphine treatment.

(2) Pregnancy and breast-feeding are listed as contra-indications for the use of buprenorphine in Australia, principally due to the lack of robust data on the safety and effectiveness of buprenorphine. For further information refer to section 5.8 on pregnancy and lactation.

(3) Severe respiratory or hepatic insufficiency.

2.1.3 Precautions

Particular caution should be exercised when assessing the suitability of buprenorphine treatment for anyone with any of the following clinical conditions.

(1) *Polydrug use.* All opioid substitution treatments should be approached with caution in individuals using other drugs, particularly sedative drugs such as alcohol, benzodiazepines, antipsychotics or antidepressants. Particular emphasis should be given to assessing the level of neuroadaptation to opioids, the likelihood of continued use of other sedative drugs, and overdose risk.

(2) *Concomitant medical conditions.* Buprenorphine is an opioid medication and caution should be exercised in using it in the following situations:

- *Recent head injury or increased intracranial pressure.*
- *Compromised respiratory function.* Buprenorphine, like other opioids, should be used with caution in patients with a sustained decrease in respiratory reserve, pre-existing respiratory depression, hypoxia, or hypercapnia such as in chronic obstructive airways disease or cor pulmonale, or sleep apnea. **In such patients, even normally safe therapeutic doses of opioids may decrease respiratory drive.**

- *Acute abdominal conditions*.
- *Severe hepatic disease.* Caution needs to be taken in considering buprenorphine treatment for people with clinically significant liver disease (i.e. acute hepatitis or cirrhosis). Severe hepatic disease may alter the hepatic metabolism of the medication. However, the presence of elevated enzyme levels on liver function testing, in the absence of clinical evidence of liver failure, does not exclude someone from treatment with buprenorphine although they will require more frequent hepatic monitoring.
- *Special risk patients.* Opioids should only be given with caution, and at a reduced initial dose, to patients with any of the following conditions:
  - advanced age or debilitation;
  - prostatic hypertrophy or urethral stricture;
  - severe renal disease (pharmacokinetic studies have not been conducted on this group, so methadone should be the first option).

(3) *Concomitant psychiatric condition.* Opioid substitution treatment should not be initiated in anyone with a psychiatric condition likely to severely compromise the capacity to give informed consent, such as acute psychosis or severe depression. The first priority should be an attempt to manage and stabilise the psychiatric condition. People at moderate or high risk of suicide should not be commenced on buprenorphine without adequate supervision, and specialist advice should be sought.

(4) *Chronic Pain*. Buprenorphine can be used as an analgesic in the management of acute and chronic pain conditions. Ideally, chronic pain is best managed under the supervision of a specialist multidisciplinary team, and appropriate referral or consultation should be considered (see section 5.7 for details of the management of patients who require analgesia while taking buprenorphine)

(5) *Transfer from methadone maintenance.* Patients taking methadone can safely transfer to buprenorphine but special precautions must be taken during dose induction in order to avoid precipitating withdrawal with the initial buprenorphine dose (see Section 3.3.2).

(6) *Low or uncertain levels of neuroadaptation to opiates.* Commencing buprenorphine in someone who is opioid dependent but not currently tolerant to opioids is justified in some circumstances where that person is likely to develop a tolerance in the near future or whose use of opioids is likely to cause them harm (prior to release from prison, for example). At other times, the degree of neuroadaptation to opioids may be uncertain. Even low doses of buprenorphine can cause sedation and respiratory depression in these circumstances. The use of concomitant sedating medications such as benzodiazepines, neuroleptics, and tricyclic antidepressants further increase this risk.

EXERCISE CAUTION WITH PATIENTS IN ANY OF THE FOLLOWING CATEGORIES

polydrug use

concomitant medical conditions (see list above)

concomitant psychiatric conditions

suffering chronic pain

transfer from methadone maintenance

uncertain neuroadaptation

2.2 Assessment procedures

A comprehensive assessment should be conducted at the outset of buprenorphine treatment. The aims of assessment are to focus on important issues and thereby start the process of patient education about risk behaviours and to start to develop a treatment plan. A comprehensive assessment can rarely be completed at the initial appointment, and generally needs to be conducted over several sessions. Initially, clinicians should target key issues important in the selection and initiation of treatment, and assess indications, contraindications and precautions. Referral or consultation with a specialist is recommended for patients with complex presentations.

2.2.1 History

(1) Drug use and treatment

- Heroin and other opioid use:
  - quantity and frequency (amount, cost, number of times used per day);
  - duration;
  - route of administration (injected/non-injected);
  - when last used;
  - features and severity of dependence.
- Use of other drugs (including benzodiazepines, alcohol, cannabis, psychostimulants) and assessment of degree of dependence on each drug class.
- History of prior attempts at withdrawal, maintenance and other treatment — what has worked and not worked before.

(2) Risk factors

- Presence of risk behaviours, particularly overdoses, self-injury, or polydrug intoxication.
- Medical and psychiatric history, with particular attention to unstable or active conditions which might potentially complicate treatment.
- Pregnancy and contraception.

(3) Social circumstances

- Home environment, social supports, employment, and barriers to change.
- Motivations and goals for treatment. Finding the right approach requires an understanding of the **reasons for seeking treatment** and of **patient goals and expectations.**

2.2.2 Examination

- Vital signs (blood pressure, pulse, respiratory rate).
- Evidence of intoxication or withdrawal from heroin or other drugs.
- Evidence of complications of injecting drug use, including injection site problems, hepatic disease, lymphadenopathy, systemic infections.
- Evidence of injection marks consistent with the stated history.

2.2.3 Investigations

- **Urinary drug screens** can be helpful in clarifying or confirming an unclear drug use history. While delays in getting the results of routine urine tests often limit their usefulness at initial assessment, conducting a urine drug screen prior to the commencement of opioid substitution therapy provides supportive evidence of opioid use that can otherwise be difficult to obtain.
- **Tests of viral serology** (HIV, Hepatitis B and C) should be considered at some stage with appropriate pre- and post-test counselling. (This is advisable after stabilisation, when the patient is better able to understand the significance and consequences of testing).
- **Liver function tests** are recommended at the commencement of treatment to establish a baseline. Periodic monitoring of liver function is also recommended.

2.3 Informed consent and patient literature

The participation of an informed patient in the clinical decision-making process is essential in the treatment of all opioid dependence. It is particularly important when incorporating opioid medications — such as buprenorphine or methadone — as part of the treatment plan. In considering the commencement of buprenorphine for maintenance or withdrawal treatment, the service provider should also explore alternative treatment options with the patient (including alternative approaches to withdrawal or substitution maintenance treatment, self-help, residential rehabilitation programs, counselling, and naltrexone).

All patients commencing treatment with buprenorphine must give their informed consent to treatment. This process requires that patients are fully informed and given an opportunity to discuss with the service provider the following topics:

- what is buprenorphine, how is it administered, how does it work, and what are its advantages and disadvantages?
- what is the duration of treatment; its cost; its associated 'routines', including urine-testing, "take-aways", transfers?
- what are the known side-effects?
- what about pregnancy and contraception issues?
- what are the dangers of additional drug use, overdose?
- what is the potential impact on driving, and on employment?
- what are the circumstances in which the doctor or pharmacist may withdraw their services and treatment may be ceased?

Specific patient literature should be provided prior to the commencement of treatment. It is recommended that consent be documented and that patients be given their own copies of the documents they have signed.

2.4 Permits and Registration of Patients

Buprenorphine is registered as a Schedule 8 medication. Each jurisdiction (See Appendix 2) is responsible for a system of authorising medical practitioners to prescribe buprenorphine to a particular patient for the management of opioid dependence within a framework of medical, social and psychological treatment.

3 Guidelines for maintenance treatment

3.1 Gateway model of treatment with buprenorphine

Patients commonly present for treatment at a time when they are in crisis. It may be that heroin use has escalated to a point of being out of control; or, sometimes, a change in their circumstances, such as an ultimatum from family, or being charged with a criminal offence, may be the precipitant to entering treatment. In these crisis situations, patients are often resolved to cease drug use and change their lifestyle. They often seek short-term treatment, without necessarily having considered all their treatment options, simply 'hoping' that an attempt at withdrawal will be sufficient to stop heroin use.

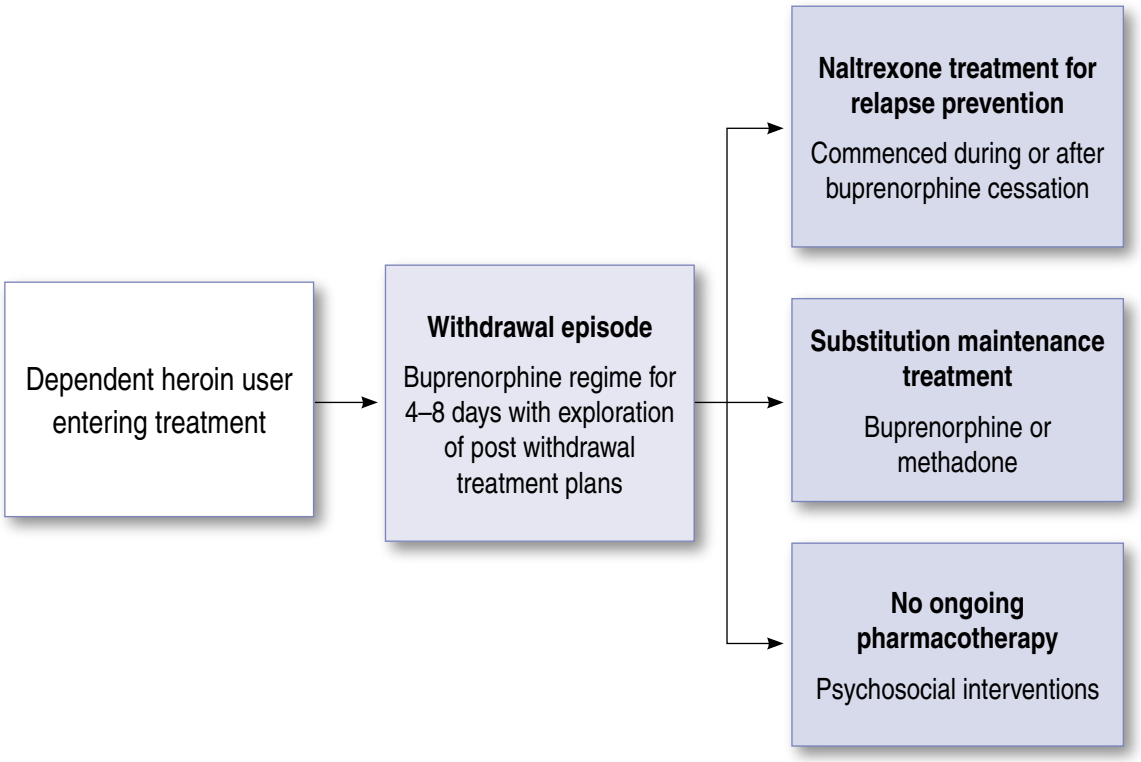
Clinical experience and research have repeatedly demonstrated that motivation to remain abstinent is often short-lived. There is strong evidence that longer-term treatment is associated with a greater likelihood of long-term abstinence from heroin than are shorter periods of treatment. Stability and consequent improvements in drug use and psychosocial stability gained as a result of opioid replacement therapy tend to become significant after three months of treatment, with the majority of benefit gained after one year (benefits may be sustained beyond this point with continued treatment). However, this is seldom what patients or their families wish to hear at the time of entering treatment. This is particularly an issue with patients requesting buprenorphine treatment, since many of them are probably seeking short-term treatment rather than maintenance. In contrast, in recent years in Australia, most patients requesting methadone are seeking maintenance treatment. Methadone maintenance is an effective alternative, and makes planning treatment more straightforward. (Readers are referred to the national guidelines for the use of methadone in the maintenance treatment of opioid dependence (Henry-Edwards *et al* 2003) for more information on this option.)

Buprenorphine is particularly useful in managing heroin withdrawal, in that it is not only effective during the withdrawal period, but also facilitates links to post-withdrawal treatment. The use of buprenorphine for several days generally alleviates withdrawal symptoms without significant sedation, thereby allowing patients and clinicians to examine post-withdrawal issues relatively early on in the withdrawal episode. (Many other withdrawal medications, such as benzodiazepines or clonidine, cause patients to be either psychologically distressed or heavily sedated such that this would not be possible.) A formal review of treatment plans should be structured several days into the withdrawal episode, at which time treatment can be tailored accordingly.

Patients who are not interested in ongoing pharmacotherapy treatment can cease after a short course of buprenorphine with minimal rebound discomfort. Alternatively, those patients who want to extend the duration of their withdrawal program, or have reconsidered the role of a maintenance treatment program, can continue buprenorphine treatment over a longer period of time.

Another benefit of buprenorphine is that naltrexone can be initiated after buprenorphine administration with less delay and less severe withdrawal than is the case following methadone maintenance treatment. These treatment pathways are shown in Figure 1.

FIGURE 1. GATEWAY MODEL OF TREATMENT WITH BUPRENORPHINE



Opioid-dependent patients who request treatment with buprenorphine, either maintenance or detoxification, and who meet jurisdictional regulations to receive buprenorphine, should be commenced on treatment as soon as possible, where this is logistically possible. Patients usually feel quite comfortable and well by the third or fourth day of treatment, and this is a good time to start exploring treatment options.

It is increasingly common for clinicians to be confronted with people requesting repeated, short-term episodes of buprenorphine treatment, perhaps three or four episodes of detoxification within a year. In this situation, where people are continually failing and relapsing, it may be more useful to recommend methadone rather than another short-term episode of buprenorphine treatment.

3.2 Selecting maintenance pharmacotherapies

Overall the research evidence suggests that key treatment outcomes for maintenance buprenorphine and methadone treatment are comparable under optimal treatment conditions, and that the difference between the buprenorphine and methadone maintenance is small compared to the variability in treatment outcomes between patients and between programs (Barnett *et al* 2001; Mattick *et al* 2003; West *et al* 2000).

Evidence for the comparative effectiveness of buprenorphine and methadone maintenance treatment has been summarised by a systematic (Cochrane) review (Mattick *et al* 2003). This review was based on 13 randomised controlled trials comparing buprenorphine maintenance with placebo or methadone maintenance. Six of these randomised controlled trials used flexible rather than fixed dosing regimes. As flexible dosing better reflects usual clinical practice, Mattick *et al.* (2003) considered data from these studies separately. They found that with flexible dosing:

- there was no difference in heroin or other drug use for either methadone or buprenorphine treatment; and
- buprenorphine patients *were* significantly less likely to remain in treatment than methadone patients (relative risk 0.82, 95% confidence interval 0.69, 0.96).

Despite the slightly greater efficacy of high-dose methadone maintenance, many patients do well on buprenorphine, and often express a preference for buprenorphine. In selecting which drug to use, such preferences are important.

Factors that might influence the choice between methadone and buprenorphine include the following.

- *Individual variation in absorption, metabolism and clearance.* There may be considerable pharmacokinetic and pharmacodynamic differences between individuals in their response to different opioid substitution pharmacotherapies.
- *Adverse events.* Individuals experiencing significant side-effects from one opioid medication may benefit from treatment with an alternative medication. In particular, buprenorphine may be preferred by individuals complaining of continued sedation under methadone.
- *Flexibility of buprenorphine treatment.* A limiting factor for many patients considering maintenance treatment is the problem of dependence on the maintenance opioid. As buprenorphine is a partial agonist and dissociates slowly from receptors, it appears to have a milder withdrawal syndrome, at least relative to heroin and morphine. It is not clear if this translates into greater success for patients discontinuing maintenance treatment. Nonetheless, buprenorphine maintenance treatment may be more likely to support attempted withdrawal. At the same time it is relatively easy to transfer from buprenorphine to methadone if a full agonist is required, and the transition from buprenorphine to naltrexone may be easier than the transition from methadone to naltrexone.

FACTORS TO CONSIDER WHEN SELECTING MAINTENANCE PHARMACOTHERAPIES

Patient preference

Response to treatment

Individual variation in absorption, metabolism & clearance rates

Adverse effects

Logistics of participating in treatments

General expectations of the treatment

Where treatment goals are not being met, a review of treatment strategies should occur, including:

- the role of psychosocial interventions,
- levels of supervision, monitoring and review,
- dose of the substitution opioid,

- the role of adjuvant interventions, and — ultimately —
- a review of alternative opioid pharmacotherapies. For example, patients who cannot stabilise their continued use of heroin, even on high doses of buprenorphine, may be better suited to treatment with high doses of a full agonist such as methadone.

3.3 Induction onto buprenorphine treatment

Research evidence indicates that the mono buprenorphine product (Subutex®) and the buprenorphine/naloxone combination (Suboxone®) formulation are largely interchangeable (See Section 1.5). Jurisdictional policies may determine the extent to which the mono and combination products are used in particular contexts, eg. takeaway dosing. There are some circumstances, eg. pregnancy, naloxone allergy, when the mono product will be preferred. Prescribers should consult responsible agencies within their jurisdiction regarding policies for use of combination or mono products.

3.3.1 Commencing buprenorphine from heroin use

The aim should be to stabilise patients on an effective dose of buprenorphine as soon as possible. More rapid dose induction (ie. 12 to 16mg by day 3) may be associated with better retention in treatment (Doran *et al* 2005). However, this needs to be weighed against individual reactions to initial dosing and safety considerations.

Rapid dose induction is most easily achieved with an initial dose in the range of 4 to 8mg. Higher initial doses will facilitate rapid dose induction but increase the risk of precipitated withdrawal (if the patient has recently used opioids) or sedation (if the patient has a lower level of opioid dependence or also consumes other sedatives such as benzodiazepines.

Patients should ideally be observed for a few hours after the first dose, and a further dose administered on the same day if there are no signs of sedation. An appropriate dose to achieve on the first day is 6 to 8mg. This may be given as a single dose or, if resources permit, in two doses, four hours apart to reduce the risk of precipitated withdrawal and adverse effects.

Prescribers should aim to achieve 12 to 16 mg/day by day 3.

Prescriptions may be written as a fixed, increasing dose regime over the first week (eg. 8mg day 1, 12mg day 2, 16mg day 3) or as a flexible regime permitting control by the patient, although the latter may result in lower maintenance doses being chosen by the patient.

The following factors must be taken into consideration when deciding the initial dose of buprenorphine:

- Time since last opioid use, and whether long-acting opioids such as methadone or slow-release oral morphine, have been taken in the last one to two days.
- *The perceived likelihood of concurrent drug abuse*, including alcohol consumption, use of prescription sedative drugs (particularly benzodiazepines), or illicit drug use. In such instances, lower doses of buprenorphine should be prescribed, with frequent reviews.
- *Concurrent medical conditions* (particularly severely impaired hepatic function and interactions with other medications) warrant the use of lower initial doses of buprenorphine with regular monitoring (see Section I "Clinical pharmacology" and Section 2.1.3 "Precautions").

The first dose of buprenorphine should be administered when the patient is experiencing early features of opioid withdrawal, at least six, and preferably 12 hours after last heroin use.

Scales for assessing opioid withdrawal, such as the Subjective and Objective Withdrawal Scales or the Clinical Opiate Withdrawal Scale (see Appendix 3) can be useful for confirming the presence of opioid withdrawal prior to administration of the first dose of buprenorphine. Opioid withdrawal will generally become apparent within six hours of heroin use. In patients who have been using slow-release oral morphine preparations, it may take 12 hours or more for withdrawal to become apparent. Particular care should be taken not to administer buprenorphine to a patient who is intoxicated on opioids.

Patients administered buprenorphine soon after heroin use may experience opioid withdrawal, as the buprenorphine displaces heroin from the opioid receptors (Clark *et al* 2002; Gourarier *et al* 1996; Jacobs & Bickel 1999; Johnson *et al* 2003). With delayed administration of the first dose of buprenorphine, as outlined above, the occurrence of withdrawal precipitated by buprenorphine will be relatively rare.

Buprenorphine precipitated withdrawal typically begins one to four hours after the first buprenorphine dose, is generally mild to moderate in severity, and lasts for up to 12 hours. If this happens, patients may require symptomatic withdrawal medication, and should be directed to see their doctor. Administration of the first dose of buprenorphine early in the day provides an opportunity to manage precipitated withdrawal if it occurs.

If precipitated withdrawal occurs following the initial buprenorphine dose, subsequent doses of buprenorphine (taken the following day) should result in light or minimal withdrawal discomfort if the patient has not used heroin during the intervening period. Patients who continue to use heroin between their first and second doses of buprenorphine may have difficulty stabilising on the treatment, with ongoing features of opioid withdrawal. They should be advised to cease heroin use at least six hours prior to the next dose of buprenorphine.

3.3.2 Transferring from methadone maintenance treatment

Transfer from methadone to buprenorphine may be appropriate when:

- side effects of methadone are intolerable;
- the patient wishes to change, perhaps in anticipation of using buprenorphine as a transitional detoxification agent, or to enable a reduced frequency dosing schedule;
- the patient has not done well on methadone;
- there are concerns over polydrug use.

There is a risk that previously stable patients may be destabilised when transferring from methadone to buprenorphine. Careful monitoring and support should be provided to any patient transferring from methadone and particularly those either reducing their methadone dose prior to transfer to buprenorphine or patients transferring from higher doses of methadone to avoid precipitating a return to illicit drug use. Transfers should be planned, considered and monitored. If they result in destabilisation, return to methadone treatment may be the best option. Transferring to buprenorphine from higher doses of methadone can also be considered (see following section on transferring from higher doses of methadone).

When methadone patients take a dose of buprenorphine, the methadone is displaced from the μ opioid receptors by buprenorphine. Patients on low doses of methadone (e.g. less than 30 mg) generally tolerate this transition with minimal discomfort. Patients on higher doses of methadone may find the replacement of methadone with buprenorphine causes significant discomfort. However, the occurrence of precipitated withdrawal can be greatly minimised by careful initial dosing and rapid titration to an appropriate maintenance dose of buprenorphine.

This has a number of clinical implications. Wherever possible, patients in methadone treatment should have their methadone dose reduced and should be stabilised on this lower dose prior to transferring to buprenorphine.

Wherever possible, patients should be on a methadone dose of less than 40mg for at least one week prior to receiving their first dose of buprenorphine. For many patients, the optimal methadone dose prior to transferring to buprenorphine may be below 30mg /day.

It is preferable for patients to be experiencing a mild degree of methadone withdrawal prior to converting to buprenorphine. This would typically occur at least 24 hours after the last dose of methadone (or at least 12 hours after the last dose of slow-release oral morphine) and is an indication that sufficient time has elapsed for there to be minimal risk that the first dose of buprenorphine will precipitate significant withdrawal. Mild withdrawal would equate to a score no greater than 8 on the Clinical Opiate Withdrawal Scale (see Appendix 3).

An initial dose of 4mg (2mg for those transferring from methadone doses above 30mg) should be given and the patient observed for one hour. If withdrawal symptoms improve, the patient can be dispensed two additional 4mg doses to be taken if needed. If withdrawal symptoms do not improve or worsen, a second dose of 2–4mg should be administered and the patient observed for another hour. If comfortable, the patient can be dispensed a further 4mg dose to be taken if needed. The prescribing doctor should contact the patient later in the day to assess the response to dosing.

This approach of repeated small doses is to be preferred. Once the buprenorphine is on the opioid receptors, the risk of precipitated withdrawal is reduced. If resources are not available for onsite dosing and regular reviews as outlined above, patients wishing to transfer from 40mg methadone or more should be referred to a specialist service.

The likelihood of precipitating withdrawal on commencing buprenorphine is reduced as the time interval between the last methadone dose and the first buprenorphine dose increases. The risk of precipitated withdrawal may be reduced by ensuring the last dose of methadone is taken early in the morning, and the first dose of buprenorphine is taken late the following day.

The first dose of buprenorphine should be administered when the patient is experiencing early features of opioid withdrawal, at least 24 hours after the last methadone dose.

There is a lack of research evidence, but the mono preparation is the preferred formulation to administer following methadone to avoid any risk of withdrawal that might be precipitated by the small amounts of naloxone that might be absorbed from the combination product. If this is thought desirable, specialist advice should be sought on the advisability of transfer and the method to do so. Once induction with the mono product is completed, the patient can be switched directly to the combination product.

Features of a precipitated withdrawal following the first dose of buprenorphine are typically mild to moderate in severity, and may distress the unprepared patient. Symptoms commence one to four hours after the first buprenorphine dose and last for up to 12 hours before subsiding. Patients experiencing discomfort may re-present to the prescribing doctor later in the day and require symptomatic withdrawal medication (e.g. clonidine 0.1mg, 3 to 4 hourly). Subsequent doses of buprenorphine (the following day) are less likely to precipitate withdrawal symptoms.

Transferring from higher doses of methadone (>40mg)

This is associated with a significant risk of precipitated withdrawal and hence is difficult in an outpatient setting. Transfer from higher doses of methadone can be safely undertaken in inpatient settings (eg. detoxification units) where supervised clonidine and diazepam can be used to manage withdrawal symptoms (Clark *et al* 2005). The critical issue in making such transfers is to wait until the patient has signs of opioid withdrawal before administering the first dose of buprenorphine. This may involve a delay of 72 hours after the last dose of methadone.

Buprenorphine can be commenced at low doses given frequently, i.e. 2mg bd increasing to 4mg bd. and then 8mg bd, titrating as necessary (Pollak 2002).

3.4 Stabilisation

The optimal maintenance dose needs to be individualised according to the patient's response to buprenorphine. However, typically a maintenance dose will be in the range of 12 to 16mg/day. People's responses vary considerably, according to the following factors:

1. rates of absorption or metabolism of buprenorphine. The duration of contact with the oral mucosa is a significant factor for the absorption of buprenorphine. Hence, instructing patients in the technique of administering buprenorphine is important.
2. experience of side-effects;
3. continued use of other drugs.

These variations require the clinician to titrate the buprenorphine dose to optimise treatment objectives.

TO ACHIEVE STABILISATION OF BUPRENORPHINE DOSE:

Regular patient review for first few weeks
adequacy of dose; withdrawal symptoms, side-effects, any additional drug use
(see below for minimal schedule of prescriber reviews).

Increase dose only as indicated by reviews
(see below for guidance on titration of doses)

Stabilisation — by the end of the first week, reported symptoms of both withdrawal and intoxication should be minimal. The optimal dose for the patient is one which is sufficient to diminish or abate the discomfort of withdrawal for the full interdosing interval, and to support a significant reduction in or cessation of other opiate use without inducing significant toxicity or side effects. Typically optimal doses at the end of the first week would be in the range of 12 to 24mg/day.

3.4.1 Regular patient review

To support regular patient review the first script for buprenorphine should be for no more than 2 weeks.

Frequent reviews by the prescriber, or delegated staff, are required in the first few weeks to:

- titrate individual optimal doses of buprenorphine,
- make a more comprehensive overall assessment of the patient; and
- further discuss treatment plans.

As treatment progresses, the prescribing doctor should review the patient two to three times a week until stabilised, to:

- establish adequacy of dose;
- inquire about withdrawal symptoms or side-effects; and
- monitor any additional drug use.

An appropriate pattern of review by the treating doctor, or a suitably trained nurse or pharmacist, is as follows:

- The day of, or the day after, the first dose of buprenorphine. This enables the prescriber to identify the onset of any precipitated withdrawal and the general adequacy of the first dose.
- Every two to four days until stabilisation.
- Every week during the following four to six weeks.
- Every two weeks during the following six to eight weeks.
- Monthly reviews thereafter, although the prescriber may wish to extend reviews to up to three months for stable patients.

Individuals with continuing high-risk patterns of drug use, or concomitant medical, psychiatric or social problems, may require more frequent review.

Maintenance buprenorphine doses should be achieved within the first one or two weeks of treatment, subject to the patient's use of heroin, or other drugs.

Dose increases should be made only after review of the patient.

If daily reviews by the prescriber or a suitably trained nurse or pharmacist can be organised, daily increases can be accommodated. Practically, however, most prescribers may not be able to review the patient more than every two or three days (e.g. because of sessional practice or weekends). A period of two to three days on a specific dose allows the patient time to get a 'feel' for their current dose, and the opportunity to modify behaviour appropriately prior to further dose changes. The buprenorphine dose may be decreased where there are concerns regarding the patient's safety (e.g. where there are reports of intoxication or overdose).

3.4.2 Changes in buprenorphine dose

Doses can be increased or decreased by between 2 and 8mg/day.

The following should guide prescribers in determining changes in the buprenorphine dose.

TABLE 4: INDICATORS OF NEED FOR DOSE ADJUSTMENT

Decrease dose if:	Increase dose if:
Features of intoxication to buprenorphine (e.g. sedation) particularly at peak effect times (1 to 4 hours after dosing)	Features of withdrawal over preceding 24 hours, increasing in the period immediately prior to the next dose (ie. not due to precipitated withdrawal)
	No features of intoxication to buprenorphine, particularly at peak effect times (1 to 4 hrs after dosing)
	Heroin use or craving
Severe or intolerable side effects (including severe precipitated withdrawal)	Nil or mild and tolerable side effects

3.5 Maintenance dosing

3.5.1 Dose levels

Effective maintenance doses, resulting in reduced heroin use and improved treatment retention, may be achieved with buprenorphine doses in the range of 8 to 24mg per day. Doses of 4mg or less will not be as effective in retaining patients in treatment or reducing heroin use (evidence suggests that such doses produce outcomes that are similar to, or worse than, the outcomes associated with methadone doses of 20mg). Most patients will require at least 12mg daily for effective buprenorphine maintenance treatment, and most patients will be able to be maintained on a dose of around 16mg/day.

Randomised controlled trials comparing buprenorphine doses have found doses of 8mg/day to be significantly more effective than 1mg/day, while doses of 12mg/day are significantly more effective than doses of 4mg/day in reducing heroin use (Ahmadi 2002; Ahmadi & Ahmadi 2003; Kosten *et al* 1993; Schottenfeld *et al* 1997; Seow *et al* 1986). A number of studies have shown a trend for 16mg to be more effective than 8mg daily (Ling *et al* 1998; Montoya *et al* 2004). This is supported by a trend for higher doses of buprenorphine (up to 32mg) to block the effects of other opioids better (Comer *et al* 2001; Greenwald *et al* 1999; Greenwald *et al* 2002; Schottenfeld *et al* 1993; Strain *et al* 2002; Walsh *et al* 1995). There has been little investigation of the efficacy of daily doses higher than 12mg compared to lower doses, and little is known regarding the nature of adverse events at maintenance daily doses greater than 32mg. Increases in the dose of buprenorphine will not necessarily result in a proportional increase in buprenorphine levels (Harris *et al* 2004).

The maximum recommended daily dose of buprenorphine is 32mg. A dose of 32mg is suitable for patients on alternate-day or four-times-a-week dosing regimes.

People wishing to reduce their use of heroin, or other opioids, can do so with increases in the dose of buprenophine, as higher doses of buprenorphine produce more effective blockade of the effects of additional heroin.

However, this only succeeds up to a point. Continued heroin use despite adequate daily doses of buprenophine may indicate that the patient needs more intensive psychosocial interventions, and/or an alternative opioid substitution (e.g. methadone).

3.5.2 Frequency of dosing: alternate-day and three-times-a-week dosing regimes

The characteristics of buprenorphine allow a wide range of dosing regimes, from several times daily to once every two or three days. The availability of the combination product, with potentially a lower risk of diversion, allows for the possibility of unsupervised dosing, which patients can be expected to manage.

Patients should first be stabilised on daily dosing. When stabilised, consideration can be given to a switch to alternate day dosing for a trial period. If the trial is unsuccessful, the patient should be returned to daily dosing. If the trial is successful, after a further period of stabilisation, further reductions in the frequency of dosing could be considered.

Evidence from 10 randomised controlled trials (Amass *et al* 1994a; Amass *et al* 1998; Amass *et al* 2000; Amass *et al* 2001; Fudala *et al* 1990; Johnson *et al* 1995; Kuhlman *et al* 1998; Perez de los Cobos *et al* 2000; Petry *et al* 1999; Schottenfeld *et al* 2000) indicates that daily and alternate daily or three-times-a-week dosing are similar in efficacy when doses are adjusted appropriately, although a few of these studies reported a non-significant trend for daily dosing to produce less withdrawal symptoms between doses and less heroin use(Amass *et al* 2000; Amass *et al* 2001; Fudala *et al* 1990; Johnson *et al* 1995; Kuhlman *et al* 1998; Perez de los Cobos *et al* 2000; Petry *et al* 2000; Schottenfeld *et al* 2000).

The main reasons for considering reduced-frequency dosing are convenience for patients, and reduced staffing requirements for supervised dose administration.

Patients suitable for a trial of reduced-frequency dosing are those:

- on a stable dose of buprenorphine for one to two weeks;
- with no high-risk drug use (ie. frequent abuse of other sedatives including alcohol, benzodiazepines, heroin or other opioids, intoxicated presentations to the pharmacy or medical practitioner, or recent history of overdose).

It is recommended that suitable patients initially be tried for two weeks on an alternate-day dosing regime of buprenorphine. If this is successful, the patient can then be tried on a three-times-a-week regime. If a patient cannot be stabilised on such dosing regimes due to the onset of withdrawal, cravings, side-effects or features of intoxication, they should be returned to a more frequent dosing regime. It is expected that less than half of patients will prefer supervised alternate day dispensing to daily supervised dispensing.

Alternate-day or four-times-a-week regime: This involves attending the pharmacy for dosing on alternate days (i.e. a dose every 48 hours), or attending four times a week (with 3 x 48 hour doses and 1 x 24 hour dose each week (e.g. Mon; Tues; Thurs; Sat)). The advantage of the latter approach (4 times a week) is that the patient is on a regular attendance each week, with less likelihood of attendance errors on the patient's part and dosing errors by the pharmacist.

The dose dispensed for a 48-hour period is initially double the normal daily (24 hour) buprenorphine dose (to a maximum of 32mg at a time). While doses higher than 32mg have been used, the registration of buprenorphine in Australia specifies a maximum dose of 32mg. More regular supervision is needed when patients are switched to less frequent dosing.

The patient should be reviewed following the first or second 48-hour dose. Dose adequacy can be inferred if patients report:

- being as comfortable on the second day as on the first;
- sleeping as well on the second night as on the day of dosing; and
- no more cravings on the second day than on the first.

If the patient reports onset of withdrawal or cravings, or sleep difficulties in the second day then the 48-hour buprenorphine dose should be increased. If the patient reports features of intoxication from the dose of buprenorphine during its peak effects (normally at about four hours), the 48-hour dose should be reduced.

Patients on low doses of buprenorphine may find that double the dose does not last for 48 hours. Patients on reducing doses of buprenorphine may need to switch to daily dosing as the dose becomes lower (i.e. below 4mg). Some patients are not comfortable with double dose when switched to less than daily dosing.

Three-times-a-week regime: Some patients may tolerate three-times-a-week dosing with buprenorphine, reducing the inconvenience and costs of treatment further. This should be attempted once a two-week trial on four-days-a-week dosing has been shown to be successful. The recommended regime for a three-day dose is:

- 3-day dose = three times the normal 24 hour dose if 24 hour buprenorphine dose < 12 mg
- 3-day dose = 32 mg when 24 hour buprenorphine dose ≥ 12 mg.

As with alternate day regimes the dose should be titrated against symptoms with frequent review following transfer to the regime. If a patient cannot be stabilised on a three-times-a-week dosing regime, the four-times-a-week dosing regime should be considered.

Some patients attempting alternate-day dosing may benefit from doses greater than 32mg, however, there is limited evidence regarding the safety of higher doses, and buprenorphine is registered in Australia with a maximum recommended dose of 32mg.

3.6 Unsupervised doses

In most jurisdictions, buprenorphine treatment assumes supervised daily administration. The objectives of supervised administration are:

- To allow close supervision and monitoring of patients;
- To minimise the risk of diversion to the black market;
- To minimise the risk of injection of crushed buprenorphine tablets;
- To minimise the risk of consumption other than as prescribed.

While supervised dosing can be an important strategy to manage risks, it can also be a serious obstacle to people participating in treatment, and an obstacle to social reintegration. Based on experience with methadone maintenance treatment, unsupervised dosing with buprenorphine can be expected to have an important therapeutic role, in:

- Improving access to treatment by reducing travel difficulties;
- Reducing congregation at dispensing points; and
- Promoting self-respect and autonomy of patients.

These guidelines for prescribing unsupervised doses of buprenorphine are based on a combination of evidence and clinical experience. They seek to assist practitioners to provide unsupervised doses while minimising these risks, by undertaking an individualised risk assessment with each patient, by undertaking appropriate patient education, and by monitoring progress after provision of unsupervised doses and reassessing their suitability over time. These guidelines attempt to emphasise process and documentation.

The process involved in deciding on suitability for unsupervised doses are assessment and consultation (optimally, with another clinician involved in the patient's care — preferably, the person who administers their buprenorphine, either a pharmacist or clinic dispensary staff). By incorporating these processes, hasty or ill-advised decisions made under pressure can be avoided. Once patients are in receipt of regular unsupervised doses, continued prescribing requires a process of monitoring and review. These processes must be documented in the patient's medical file.

Specific policies on the provision of unsupervised doses of buprenorphine will be determined by each jurisdiction. (See Appendix 2). There are three broad domains to take into account in assessing suitability for unsupervised doses:

- Continued dependent use or abuse of drugs (opioids, benzodiazepines, alcohol, psychostimulants) is a contraindication to providing regular unsupervised doses.
- Risk assessment — several situations are contraindications to prescribing unsupervised doses, and others are relative contraindications.
- Access issues — where access to buprenorphine is compromised by geographical factors or work commitments, and reducing the frequency of supervised dosing to alternate days or three times a week is not acceptable, there are grounds for prescribing unsupervised doses as long as there are no contraindications.

Indications of stable drug use

Drug use is assessed by:

1. clinical examination (inspection of veins, signs of alcohol abuse);
2. presentations for dosing while intoxicated (confirm with dispensing point);
3. random urine drug screening (self-report is of limited value where unsupervised doses are contingent on absence of illicit drug use);
4. liver function tests can be useful in monitoring alcohol abuse in that elevated gamma-glutamyl transferase (GGT) is unusual in chronic viral hepatitis, and suggests excessive drinking;
5. evidence of doctor shopping from Medicare Australia (formerly the Health Insurance Commission) or a Pharmaceutical Benefits Scheme safety net entitlement card.

Stable drug use, and suitability for unsupervised dosing, is indicated by:

- Regular attendance at appointments;
- Urine drug screens provided when requested;
- No or infrequent additional opioid use;
- Benzodiazepine use is absent or at low levels (<30mg/day diazepam equivalent) and stable;
- No alcohol abuse;
- No or infrequent use of stimulants;

- No intoxicated presentations or overdoses in prior three months;
- No missed doses in past four weeks.

Risk assessment

Circumstances where there is a high risk associated with unsupervised dosing include:

1. Unstable accommodation and living arrangements (for example, partners/friends who are actively injecting, unsatisfactory arrangements for storage of dose);
2. In buprenorphine maintenance treatment for less than three months;
3. Moderate risk of self-harm;
4. Children under six at risk because of domestic violence, parenting difficulties, emotional or sexual abuse, mental health problems or the parent's reluctance to engage with maintenance treatment;
5. Evidence of diversion of doses;
6. History of seeking a replacement dose for lost takeaway doses.

The "one-off" supervised multiple dose: In circumstances where a patient is ineligible for buprenorphine take-aways (e.g. recently commenced treatment, high-risk drug use), but is unable to attend for dosing for one or two days, it is possible to administer a **supervised** dose of buprenorphine that is two or three times the normal daily dose (as administered to patients engaged in alternate-day or three-times-a-week dispensing). In this way, occasional inability to attend the pharmacy for one or two consecutive days can be managed without the use of take-away doses.

3.7 Ancillary interventions

People with a background of heroin dependence often have a range of social problems (e.g. financial, employment, parenting, legal, accommodation) and psychological difficulties (e.g. depression, anxiety). The stability afforded by long-term substitution treatment provides an opportunity for these issues to be addressed. It is one of the key roles of treating clinicians to assist in this process, either as direct service providers, or as case managers referring the patient on to appropriate services for other areas of their lives.

There has been considerable debate over the role of counselling in maintenance substitution programs. The evidence from methadone treatment studies suggests that counselling should be available to all patients, and that patients should be actively encouraged to avail themselves of counselling services.

Once opioid use is stabilised, prescribing doctors need to monitor for the presence of, or emergence of, other concurrent problems, particularly mental health issues. Such monitoring and documentation of response to treatment is a critical part of effective treatment.

3.8 Continued high-risk drug use

People are said to be in continued high-risk drug use when there are frequent presentations while intoxicated or overdoses of heroin or other substances, frequent missed doses, chaotic drug-related behaviours, or deteriorating medical or mental states due to drug use.

Attempts should be made to stabilise such patients. A review is required of their psychosocial interventions and supports, precipitants to continued drug use, and medication regimes.

An adequate dose of buprenorphine should be prescribed and the clinician must ensure that the patient is taking the buprenorphine as prescribed, which may require:

- ceasing take-away doses;
- ensuring supervised consumption;
- daily dosing regimes; and
- drug testing (eg. on-site urine screens).

Increases in the dose of buprenorphine may assist patients to reduce their heroin use.

Transfer to another pharmacotherapy (e.g. methadone) may be indicated if:

- there is little or no response to an increase in medication;
- the patient is already on a high dose of medication;
- an increase in dose is considered 'unsafe' by the prescriber;
- the patient is persistently diverting their dose; or
- the patient attends irregularly, frequently missing scheduled doses.

Alternatively, non-pharmacotherapeutic treatment options should be considered (e.g. therapeutic communities, counselling and support), and the patient withdrawn from prescribed opioid medication.

3.9 Missed doses

Sometimes a patient who is on an alternate-day or three-times-a-week regime misses a 'dosing day', and attends on the following ('non-dosing') day. When this happens, a lower dose of buprenorphine should be prescribed and dispensed in order to tide the patient over until the next scheduled dose.

The following procedures are recommended:

- The pharmacist should contact the prescriber. The buprenorphine dose prescribed should be sufficient to last until the next scheduled dose (if this is 24 hours, then prescribe a 24-hour dose; if 48 hours, prescribe a 48-hr dose).
- In circumstances where the pharmacist cannot contact the prescribing doctor, no buprenorphine can be dispensed (as there is no valid prescription). However, this increases the risk that the patient will drop out of treatment. To prevent this happening, the prescriber can issue a prescription of buprenorphine to be administered by the pharmacist as a **one-off dose,** for use if a patient on a three- or four-times-a-week regime misses the scheduled dosing day and presents on a non-scheduled day.

This prescription **must not be greater than the usual 24-hour dose**. The prescriber may wish to limit the maximum level of such an 'emergency dose' to a lower than usual dose in order to discourage such occurrences.

Patients who have erratic attendance for dosing are unlikely to achieve optimal outcomes. Patients who repeatedly miss doses under these circumstances should be reviewed by their prescribing doctor to find out why, and whether these issues can be addressed. Alternatively, consideration might be given to a more feasible dosing regime.

Patients who have missed more than one week of dosing should be reinducted into buprenorphine treatment. Those who have missed less than one week can be continued on their maintenance dose, after being reviewed by their prescribing doctor and provided there is no evidence of acute intoxication with opioids, alcohol or benzodiazepines.

3.10 Cessation of buprenorphine maintenance treatment

Nature of withdrawal from buprenorphine maintenance treatment

Research evidence regarding the nature and severity of withdrawal following cessation of buprenorphine maintenance treatment, remains limited. The symptoms and signs of withdrawal from buprenorphine are qualitatively similar to withdrawal from other opioids. The withdrawal syndrome on cessation of buprenorphine is delayed and may be milder than withdrawal from heroin, morphine and methadone (Amass *et al* 1994b).(Cami *et al* 1991; Horgan 1989; Jasinski 1981; Jasinski *et al* 1982; Mello & Mendelson 1980; Mudric *et al* 1998; Resnick *et al* 1992; Sam *et al* 1991; San *et al* 1992)

A common pattern of withdrawal following cessation of buprenorphine maintenance treatment is as follows:

- The onset of symptoms is usually around 24 to 72 hours after the last 24-hour dose.
- Symptoms peak around days three to five following short maintenance courses of buprenorphine treatment (weeks to months), or days 5 to 14 for longer-term treatment.
- Duration of withdrawal from buprenorphine maintenance treatment has not been established, although mild to moderate withdrawal symptoms (particularly cravings, sleep and mood disturbances associated with protracted withdrawal) may persist for weeks. One study described mild but ongoing withdrawal features 30 days after the last buprenorphine dose. Longer-term follow up has not been reported.

Voluntary withdrawal from buprenorphine maintenance treatment

The decision to withdraw from opioid replacement therapy, preferably after a period of improved functioning associated with a marked reduction in illicit use should be made collaboratively between the patient, the doctor and the case manager, with information contributed by others involved in the patient's care.

A patient may wish to withdraw from maintenance treatment for a range of reasons, e.g. the need for interstate travel, concerns about side-effects or about remaining in treatment 'too long'. The clinician should address issues regarding the duration of treatment and withdrawal early in the treatment program, and provide information regarding the process of withdrawal.

The likelihood of premature withdrawal from maintenance treatment is reduced by ensuring patients are well-informed about the maintenance program.

Dose reduction from maintenance buprenorphine with the ultimate aim of achieving a period of abstinence from opiates needs to be planned and delivered within a period of stability and sustained motivation.

Before commencing a reduction in buprenorphine dose, the clinician should assess the patient and determine their motivation, psychosocial stability, current alcohol and drug use, expectations, source of support, concerns, and aftercare plans. A treatment plan for withdrawal should be developed, including the pattern of dose reduction, and preparation for withdrawal (eg. removing paraphernalia, informing significant others, avoiding stressors etc). Information should also be provided to the patient about the nature and severity of the withdrawal symptoms from buprenorphine.

Contraindications to dose reduction and withdrawal include:

- irregular attendance at the dispensing site for dose pick-up;
- non-attendance at case review meetings;
- significant current psychological problems or social instability or distress (eg. acute mental health problem, bereavement, homelessness);
- significant current opiate or other substance use (as indicated by self-report or drug testing).

When abstinence is an immediate goal, withdrawal from maintenance can generally be achieved in periods of two to eight weeks, depending on starting dose and the rate of dose reduction. Most dose reductions can take place safely and effectively within the community with dosing from either a public clinic or pharmacy.

Dose reduction regimes can be planned to address variables such as starting dose, duration of time on maintenance, the timeframe and circumstances of the patient with an overall aim of minimising discomfort and maximising the chance of the patient achieving their aims. The patient should be assured that the rate of reduction can be changed if the patient experiences difficulties, eg. intolerable withdrawal, stressors, or resumption of regular opiate use.

TABLE 5: RATES OF DOSE REDUCTION

Dose of buprenorphine	Reduction rate
Above 16 mg	4 mg per week or fortnight
8–16 mg	2–4 mg per week or fortnight
Below 8 mg	2 mg per week or fortnight

Studies suggest that more gradual tapers are more effective than more rapid ones (Amass *et al* 1994b; Becker *et al* 2001). More rapid dose reduction may be considered in those who only had a recent brief period of treatment or when circumstances make rapid dose reduction desirable. More rapid dose reduction when conducted on an outpatient basis should only be conducted when there is significant support and opportunity for review.

The patient should be assured that the rate of dose reduction can be changed in the event of difficulties eg. intolerable withdrawal, stressors or resumption of regular opioid use. Some patients will request dose reductions of less than 2mg. Reductions of 0.4 to 0.8mg per week or fortnight may then be appropriate, especially for those coming off longer-term buprenorphine treatment.

Supportive care

Increased supportive counselling, as well as information and education, should be available for patients withdrawing from buprenorphine. There may be a role for other medication for symptomatic relief. These include clonidine, NSAIDs, anti-emetics, and anti-diarrhoeal agents.

Involuntary withdrawal

The conditions for involuntary termination (without patient consent or against patient's wishes) usually concern behaviour which the service provider finds intolerable, and will vary from program to program. These may include:

- threatened or actual abuse of other patients or staff;
- illegal activities, such as theft, property damage, or drug-dealing, in or near the service;
- diversion of medications;
- poor compliance with treatment;
- no reduction in on-top opioid use.

The rate of reductions under circumstances of involuntary treatment cessation can be faster (e.g. up to 4 to 8mg reductions every 3 to 4 days). Patients who pose a considerable risk to the safety of other patients or staff may be abruptly terminated without a graduated dose reduction.

Transfer to other service providers should always be considered as an alternative to rapid involuntary discharge.

Commencing naltrexone following buprenorphine maintenance treatment

To minimise the risk of withdrawal symptoms, naltrexone should be delayed for 5–7 days after the last buprenorphine dose. Doses of naltrexone taken earlier than this are likely to induce some withdrawal symptoms depending on the buprenorphine doses in the last few weeks and the timing of the first naltrexone dose (Eissenberg *et al* 1996; Kosten *et al* 1991; Rosen & Kosten 1995; Umbricht *et al* 1999). Naltrexone (12.5mg) taken within one to three days of the last buprenorphine dose (2mg or more) may induce a severe withdrawal syndrome (Clark *et al* 2005a). If transfer to naltrexone is required in less than five days advice should be sought from a specialist service.

The following procedures are recommended.

- Where the maintenance dose of buprenorphine is less than 6mg for at least a week, the first dose of naltrexone can be commenced within 24 hours of cessation of buprenorphine in an inpatient setting capable of managing severe withdrawal symptoms including dehydration and delirium. Outside of this setting, or if the maintenance dose is greater than 6mg, the use of naltrexone is not recommended within seven days as it may induce severe withdrawal features.
- The initial dose of naltrexone (12.5 mg orally) should be administered in the morning. The patient should be monitored for up to 3 hours after the first dose of naltrexone for features of opioid withdrawal.
- Symptomatic withdrawal medication should be available for the patient to use in the 12 hours after the first dose of naltrexone, including clonidine (0.1–0.15mg, 3–4 hourly), benzodiazepines (e.g. diazepam up to 5–10 mg every 3–4 hours as needed), metoclopramide, hyoscine butylbromide and NSAIDS.
- Subsequent doses of naltrexone at 25mg for a further 2–3 days and then 50mg per day is usually recommended. Clinical guidelines regarding the use of naltrexone should be consulted (Bell *et al.* 2003).

Given the potential for patients to use heroin or other opioids following the cessation of buprenorphine and prior to the commencement of naltrexone, some objective test should be conducted prior to commencing naltrexone in order to exclude recent opioid use. **The naloxone challenge test or appropriate urine drug screening are recommended. However, a naloxone challenge test is difficult to interpret if conducted within three days of buprenorphine use.**

Transferring to methadone

Consideration should be given to transferring a patient from buprenorphine to methadone under the following circumstances:

- Intolerable side effects to buprenorphine.
- Inadequate response with buprenorphine treatment. Treatment with buprenorphine should be considered unsuccessful if it has not resulted in marked improvements in the patient's drug use, injecting risk practices or other outcomes identified by the patient and clinician as treatment goals. In such instances, treatment with an alternative substitution pharmacotherapy should be considered.
- Buprenorphine is not available. As buprenorphine is a relatively new drug, it may not be available in certain jurisdictions, when the patient is overseas, during periods of incarceration and in some hospitals. Patients should be transferred to methadone in such circumstances. To facilitate the subsequent return to buprenorphine treatment (if planned), the lowest effective methadone dose should be used.
- Complications with antagonists and analgesics. In patients who have frequent overdoses, the use of buprenorphine may complicate resuscitation efforts with naloxone. Such patients should be taken off substitution pharmacotherapies or transferred to methadone. Patients requiring frequent opioid analgesia for recurrent acute or chronic pain conditions may be better stabilised on full agonists, such as methadone.

Transferring from buprenorphine to methadone treatment is less complicated than the transition from methadone to buprenorphine. Methadone can be commenced 24 hours after the last dose of buprenorphine, at an initial maximum daily dose of 40mg. It is recommended that the doctor review the patient several hours after the first dose of methadone to adjust the subsequent doses accordingly.

Methadone can be commenced 24 hours after the last dose of buprenorphine, at an initial maximum daily dose of up to 40mg.

Patients transferring from low doses of buprenorphine (e.g. 4mg or less) should be commenced on lower doses of methadone (e.g. 20mg methadone or less). The methadone dose can then be titrated accordingly. Care should be taken when increasing the dose of methadone, as buprenorphine may diminish the effects of methadone for several days (blockade effect), and there should be adequate time to allow "wash out" of buprenorphine prior to marked increases in methadone dose.

4 Guidelines for the management of heroin withdrawal

4.1 Heroin withdrawal in context

Heroin withdrawal defined

Drug withdrawal is a substance-specific syndrome due to the cessation or reduction of heavy and prolonged drug use. This syndrome causes clinically significant distress and impairment in social, occupational, or other important areas of functioning. The characteristic features of heroin withdrawal are shown in table 6.

TABLE 6: CLINICAL FEATURES OF THE HEROIN WITHDRAWAL SYNDROME

Increased sweating, lacrimation, rhinorrhoea, urinary frequency
Diarrhoea, abdominal cramps, nausea, vomiting
Muscle spasm leading to headaches, back aches, e.g. cramps, twitching, arthralgia
Piloerection, pupillary dilatation, elevated blood pressure, tachycardia
Anxiety, irritability, dysphoria, disturbed sleep, increased cravings for opioids

Physical symptoms generally commence 6 to 24 hours after last use, peak in severity during days two to four, and generally subside by day seven, while the psychological features of dysphoria, anxiety, sleep disturbances and increased cravings may continue for weeks or even months. Heroin withdrawal is unpleasant, though rarely, if ever, life-threatening in physically fit people. It can, however, significantly complicate concomitant medical or psychiatric conditions.

Objectives of withdrawal services

Heroin users present to withdrawal services for a range of reasons and motivations, and the goals of individual patients may vary considerably. Withdrawal services should not be seen as a stand-alone treatment that is likely to result in prolonged periods of abstinence, but instead as a transitional step on the long road to abstinence. Indeed, research suggests that withdrawal treatment alone has little, if any, long-term impact on levels of drug use (Mattick & Hall 1996; Vaillant 1988). Unfortunately, many patients, families, friends, and health and welfare professionals hold unrealistic expectations regarding the outcomes of withdrawal services. Many are disappointed when people in these programs either cannot give up their heroin use in the first place, or recommence regular heroin use soon after a withdrawal attempt.

Set sensible withdrawal objectives with the patient and their carers

A realistic set of objectives for withdrawal services is as follows:

1. *To alleviate distress.* Palliation of the discomfort of heroin withdrawal symptoms is an important reason for patients presenting for treatment, and one of the primary aims of withdrawal services.
2. *To prevent severe withdrawal sequelae.* Although heroin withdrawal on its own is almost never life-threatening, withdrawal can present various serious problems:
   - Complication of concomitant medical or psychiatric conditions, e.g. precipitation of an acute psychotic episode in a patient with schizophrenia in remission, Wernicke's encephalopathy in alcoholics or dehydration in an individual with poor baseline nutritional status or diabetes.
   - Increased risk of overdose following withdrawal. This can occur with resumption of heroin use following the reduction in opioid tolerance that accompanies withdrawal, and due to the combined sedative effects of heroin use and medications used for the management of heroin withdrawal (e.g. benzodiazepines).
3. *To provide linkages to and enable engagement in ongoing treatment.* Withdrawal services are essentially acute services with short-term outcomes, whereas heroin dependence is a chronic relapsing condition, and positive long-term outcomes are more often associated with longer participation in treatment. Consequently, an important role of withdrawal services is to provide links with post-withdrawal services for those with other physical problems, or psychological or social needs. Optimally, they should have automatic access to drug treatment services, such as 'drug-free' counselling; naltrexone treatment; residential therapeutic communities; self-help programs; or substitution maintenance programs with methadone or buprenorphine. Managed withdrawal provides an opportunity to plan longer-term treatment and be linked to appropriate services. The boundaries between buprenorphine treatment to manage withdrawal and maintenance can be blurred — people who continue using heroin during withdrawal should be encouraged to consider transfer to maintenance treatment.
4. *To break a pattern of heavy and regular drug use.* Many patients want treatment to end their heroin use completely during the withdrawal episode, intending to stay off heroin for a set period of time afterwards. However, giving up entirely is not the goal of every patient.
5. *To get help with any other problems.* While some people will be unwilling or unable to continue in ongoing drug treatment programs, they may need — and be grateful for — contacts with welfare services (e.g. accommodation); general support and case management services (e.g. outreach workers); or primary or specialist health services.

4.2 Non-pharmacological aspects in the management of heroin withdrawal

As well as the use of medications (pharmacotherapy) the delivery of withdrawal services entails:

- assessment,
- treatment-matching,
- planning for withdrawal,
- supportive care, and
- linkages to services for further treatment and support.

The assessment of patients presenting for treatment was discussed in Section 2.2.

Treatment selection

Treatment selection is a synthesis of:

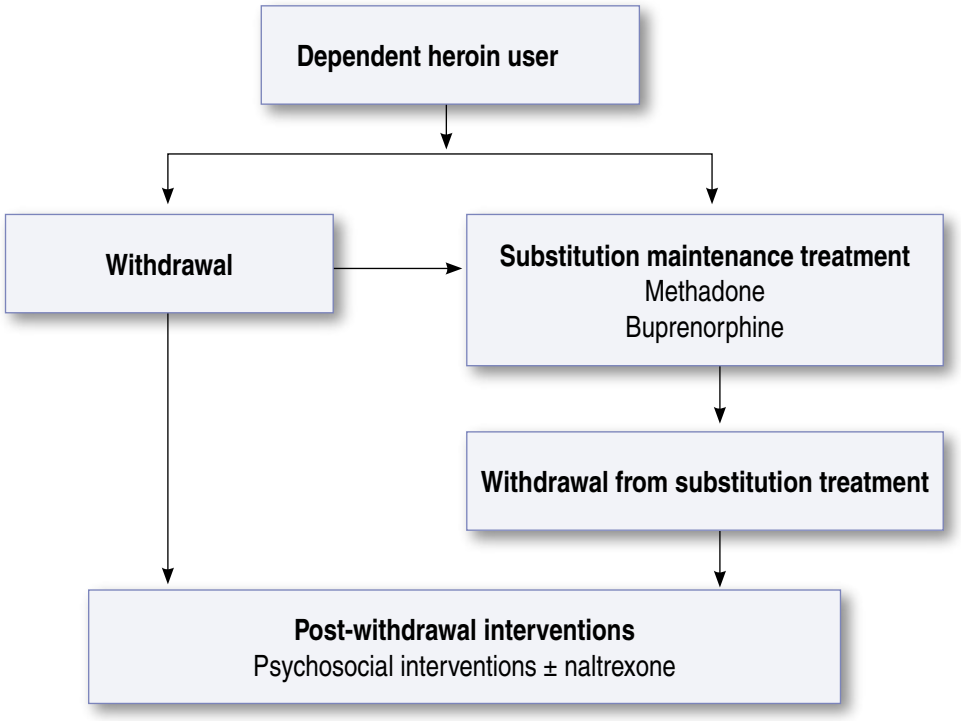
- assessment of the patient;
- examination of the available treatment options and likely outcomes; and
- negotiation with the patient around a suitable treatment pathway.

In considering possible modalities, it is important to remember that many people come for treatment with misconceptions and/or inadequate information about the two major options available. These treatment pathways for dependent heroin users are set out in Figure 2.

In general, withdrawal treatment is appropriate for those who are considering abstinence-oriented, post-withdrawal treatment (such as naltrexone, residential rehabilitation programs, counselling or 12-step programs), or for those who are not interested in longer-term treatment, and merely want a 'break' from dependent heroin use.

However, maintenance substitution treatment (with methadone or buprenorphine) may be more appropriate for those with significant heroin dependence who will not accept residential rehabilitation or naltrexone treatment, but nevertheless want to stop or permanently reduce their heroin use and all the damage it is causing them.

FIGURE 2: TREATMENT PATHWAYS FOR DEPENDENT HEROIN USERS



Clinical decision-making should have an evidentiary basis, and patients should be presented with the relative evidence, i.e. the merits and the limitations of treatment outcomes associated with each approach. Within such a framework, there is widespread evidence suggesting that maintenance substitution remains the 'gold standard' treatment for most people with chronic heroin dependence, by virtue of its success in keeping patients in treatment, and reducing drug-related harms.

Once it is established that withdrawal is to be attempted, consideration must be given to the services needed to achieve the best outcome. An optimal setting and adequate supports should be found for each patient, and monitoring arranged for their personal requirements and medication needs.

The optimal setting for withdrawal

Withdrawal can occur in a continuum of settings, ranging from intensive residential (e.g. inpatient withdrawal unit or hospital) to outpatient (e.g. ambulatory or home-based withdrawal services). Most heroin withdrawal attempts can occur in outpatient settings, usually with the assistance of a general practitioner, alcohol and drug worker, or other health professional. However, there are circumstances where a residential setting is indicated (see Table 7).

Some patients may wish to persevere with an outpatient withdrawal, despite unsuitable home environments or having repeatedly 'failed' as outpatients before. Such attempts at outpatient withdrawal may still be appropriate, however clinicians should first negotiate with their patient some mutually agreed criterion of failure (e.g. no significant progress within a week) at which point consideration of a switch will be made to an alternative treatment pathway.

TABLE 7: COMPLEX PRESENTATIONS REQUIRING RESIDENTIAL WITHDRAWAL SERVICES

Criteria for intensive residential settings (e.g. inpatient withdrawal unit)
• Unstable medical / psychiatric condition; • Polydrug dependence and withdrawal from multiple drugs; • History of medical or psychiatric conditions, or past drug use, uncertain or indicate a need for close monitoring.
Criteria for supported residential setting (e.g. community withdrawal unit)
• Unsupportive home environment, such as with other drug users, or without anyone reliable to supervise and support the patient; • Repeated failure at outpatient withdrawal.

Getting organised for withdrawal

Residential withdrawal settings generally provide the full range of services needed for a withdrawal episode. They set out to be drug-free, with support available from staff and fellow patients, and the capacity for continuous monitoring. They usually have access to medical staff and medications. Patients on a waiting-list may need short-term support in the interim.

Commencing an outpatient withdrawal requires planning, and the mobilisation of the necessary supports and services. Patients should prepare themselves and their environment in advance, to maximise their chance of 'success'. For example, it is very hard to get through withdrawal in the company of others still using heroin.

A safe environment should be organised at the beginning of the withdrawal episode.

A 'safe' place is one where there won't be any drugs easily accessible, and where patients will not be confronted by other drug users. It is important to have caring people to support a patient during withdrawal, and these support people themselves need guidance and information about the process, and suggestions as to what they can reasonably do to help.

Supportive care

Patients need information regarding:

- the nature and duration of withdrawal symptoms;
- strategies for coping with symptoms and cravings;
- strategies to remove high-risk situations;
- the role of medication.

Patients often have limited concentration during withdrawal, and information may have to be repeated, perhaps even re-phrased, to be fully understood and absorbed. Written information is valuable in these circumstances, and is also recommended to support patients and their relatives people (contact the local drug and alcohol authority for relevant literature).

Counselling during the withdrawal episode should be aimed specifically at supporting the patient through problems associated with withdrawal and in facilitating post-withdrawal links.

Many patients will want to deal with a range of personal, emotional or relationship problems during the withdrawal episode, but they should be persuaded to defer all this until later. Attempting to work through such issues will almost certainly be emotionally painful and anxiety-provoking, which just intensifies cravings and withdrawal and puts the whole withdrawal program in jeopardy. Furthermore, patients in withdrawal tend to be irritable, agitated, tired and run-down; they can suffer from mood swings and poor sleep patterns, as well as having difficulty in concentrating. This is definitely not the optimal frame of mind in which to try to solve significant, long-standing life problems. Assure your patients that you understand that they have many important issues to work through to get their lives together again, but it is best to take one step at a time. There will be opportunities for these wider problems to be addressed as part of their ongoing rehabilitation after they get through withdrawal. On the other hand, crisis intervention may be required during a withdrawal episode to ensure adequate accommodation, food or other urgent welfare issues.

In addition to supportive counselling from health professionals and the support of family, friends and peer workers, heroin users may also benefit from 24-hour telephone counselling services for help when others are unavailable. Each state in Australia has telephone alcohol and drug services (see Appendix 2).

Monitoring

An important part of withdrawal services is regular and frequent monitoring, to check:

- general progress;
- drug use;
- response to the medication(s);
- severity of withdrawal symptoms (which can be facilitated by the use of withdrawal scales);
- complications or difficulties;
- ongoing motivation levels.

Doses of medication can then be adjusted according to the patient's progress. It is recommended that patients undergoing outpatient withdrawal be reviewed by a health professional (e.g. alcohol and drug worker, general practitioner, or experienced pharmacist) **at least daily** during the first few days of treatment.

Scales for assessing opioid withdrawal

There are various opioid withdrawal scales available to refer to. Subjective scales are far more sensitive to changes in withdrawal severity, and are better predictors of patient outcomes. Objective scales are not only less sensitive, but usually need to be administered by a health professional. They may nevertheless be useful in corroborating subjective ratings, particularly in individuals who are thought to be over- or under-rating their withdrawal severity. Copies of several scales that are commonly used in Australia and overseas are provided in Appendix 3.

4.3 Overview of buprenorphine in the management of heroin withdrawal

Efficacy of buprenorphine compared to other withdrawal medication regimes

A systematic (Cochrane) review (Gowing *et al.* 2006) of controlled trials found that:

- buprenorphine is more effective than clonidine in ameliorating withdrawal signs and symptoms, and is associated with a significantly higher rate of completion of treatment;
- there appears to be no significant difference between buprenorphine and tapered methadone in terms of completion of treatment, but withdrawal symptoms may resolve more quickly with buprenorphine.

These conclusions applied to both inpatient and outpatient settings.

Buprenorphine for the management of withdrawal in the medically ill

Uncontrolled studies have reported favourably on the use of buprenorphine for the management of heroin withdrawal in medically-ill patients (Parran *et al* 1994). One randomised controlled trial found buprenorphine to be as effective as clonidine and methadone for the short-term management of withdrawal in heroin-dependent HIV-infected patients hospitalized for medical reasons on an inpatient AIDS unit (Umbricht *et al* 2003). These studies suggest buprenorphine is of potential value in the management of withdrawal in the medically ill. Furthermore, the sublingual preparation is well suited to individuals who cannot tolerate oral medications. Caution should be used in using buprenorphine or other opioids in individuals with certain medical conditions (see Section 2.1).

The role of buprenorphine in withdrawal

The aim of medication in withdrawal is the reduction of withdrawal symptoms and cravings; it is not the complete removal of all symptoms. The clinician should discuss patients' expectations of the medication with them, and address any misconceptions.

In particular, the following principles regarding doses should be understood by the patient:

- Buprenorphine doses that are too high can result in increased rebound withdrawal, prolonged duration of symptoms, increased side-effects, and increased cost of the medication.
- Alternatively, use of doses that are too low can result in unnecessary withdrawal discomfort, continued heroin use and treatment drop-out.

- Continued heroin use or cravings may not be due to inadequate doses of medication. For example, patients who continue to associate with other heroin users, and are present when others are acquiring or using heroin, can expect to have cravings regardless of their dose of buprenorphine.
- Buprenorphine will not reduce symptoms of withdrawal, or cravings, related to the use of non-opioid drugs.

Preventing precipitated withdrawal on commencing buprenorphine

Buprenorphine can precipitate opioid withdrawal in someone who has recently used heroin (within the past 6 hours), slow-release oral morphine (within the past 12 hours) or higher doses of methadone (See Section 3.2). Buprenorphine-precipitated withdrawal typically commences one to four hours after the first buprenorphine dose, is generally mild to moderate in severity, and lasts for up to 12 hours. Patients experiencing severe discomfort may benefit from symptomatic withdrawal medication (e.g. clonidine 0.1mg, 3 to 4 hourly as required), and should be directed to see their prescribing doctor.

Patients should not receive the first dose of buprenorphine if they are experiencing heroin effects. It is preferable to withhold the first dose until the patient is beginning to experience the early features of withdrawal. Typically this will occur six hours or more after their last use of heroin. If there are doubts or concerns, the patient should be asked to come back for dosing later in the day, or alternatively, a lower initial dose can be dispensed (e.g. 2 or 4 mg) as it is less likely to precipitate significant withdrawal than a high initial dose.

Preventing precipitated withdrawal on commencing buprenorphine

No heroin for at least 6 hours: severe discomfort may need palliation.

No methadone for at least 24 hours.

No buprenorphine if there are obvious heroin effects: wait for early withdrawal signs, or send away to return next day.

Use of ancillary medications in conjunction with buprenorphine

Buprenorphine provides general relief of withdrawal symptoms, so that other symptomatic medications for opioid withdrawal are not routinely required. An exception is when patients experience difficulty sleeping during withdrawal, and may benefit from the limited use of benzodiazepines as a hypnotic. Benzodiazepines should not be used routinely from the outset of the withdrawal episode. Where sleep is a problem, it is safer to increase the dose of buprenorphine than to prescribe benzodiazepines, with non-pharmacological approaches being encouraged (sleep hygiene strategies). Non-pharmacological methods may not have an instant effect on sleep, but if continued for days to weeks such strategies will help establish normal sleep patterns.

Continued use of heroin and other drugs

Patients who keep on using heroin during buprenorphine treatment may have difficulty stabilising on the medication, and may continue to experience features of precipitated withdrawal after each dose.

Persistent features of precipitated withdrawal discomfort may be grounds for transfer to methadone, or other withdrawal medications.

The unsupervised use of other sedative drugs, such as benzodiazepines, alcohol, other opioids, tricyclic antidepressants, and sedative antipsychotics in combination with buprenorphine, can be extremely dangerous, resulting in respiratory depression, coma and death.

All patients should be informed verbally and in writing of these risks, and this advice documented in the clinical records. Intoxicated patients should not be dosed with buprenorphine or sedative medications.

4.4 Buprenorphine regimens in outpatient withdrawal settings

Buprenorphine is long-acting, and so is well suited to outpatient withdrawal settings, allowing for once-a-day supervised dosing.

Take-away doses are not recommended during the initial treatment period, and are subject to jurisdictional regulations.

Patients unable to attend an authorised pharmacy daily for supervised dispensing should consider alternative withdrawal medications.

There is no conclusive evidence of an optimal buprenorphine dosing regime for heroin withdrawal. In general, daily buprenorphine doses of 4 to 16 mg appear to be most effective in reducing withdrawal severity and heroin use (Gowing *et al.* 2006).

Induction onto buprenorphine for the purposes of detoxification should follow the same principles as for buprenorphine maintenance. Reductions of the buprenorphine dose should not be commenced until the patient has received a dose that virtually abolishes withdrawal symptoms for 24 hours.

Some flexibility in doses is allowable to accommodate a range of factors, such as amount of heroin use and psychological condition, which may impact on each patient's individual dosing requirements and withdrawal severity.

Review by a trained health professional is recommended on a daily basis during the first few days of the withdrawal regime. This is important so that doses can be adjusted, if necessary, and any difficulties being experienced on the medication can be addressed. It is also needed to ensure provision of appropriate support, care and monitoring.

Buprenorphine doses should be titrated against severity of withdrawal features and cravings for heroin use, actual use of heroin or other drugs, and occurrence of side-effects and intoxication.

Doctors may choose to prescribe a fixed daily dose (e.g. Day 1: 6 mg, Day 2: 8 mg, Day 3: 10 mg etc) or, alternatively, prescribe a flexible regime with upper and lower limits on any particular day and instructions for the pharmacist or withdrawal worker regarding dose titration (e.g. Day 1: 6 mg, Day 2: 6–10 mg; Day 3: 8–12 mg etc).

The planned duration of withdrawal treatment should be guided by the patient. Most commonly the duration of buprenorphine administration will be between five and 20 days.

Longer-term reduction regimes (over 2 to 3 weeks) permit more time for relapse prevention and after-care planning, but there are good reasons for preferring a short-term withdrawal regime (4 to 5 days) and not prolonging buprenorphine treatment:

- Administration of buprenorphine for more than several days may be associated with rebound withdrawal when ceased (Lintzeris 2002). Such rebound withdrawal typically starts one to three days after the last dose of buprenorphine, and peaks two to five days after the last dose, with some symptoms persisting for several weeks.
- Prolonged, probably unsuccessful, attempts at withdrawal can be demoralising for the patient, resulting in lowered capability, self-esteem, and/or confidence in the treatment provider. For this reason, a limit on the time spent on a gradual reduction regime should be discussed with the patient early in the program.

A formal review of progress should be scheduled partway through an outpatient withdrawal program. At the time of the review, those patients who remain ambivalent about long-term post-withdrawal treatment, and who have not been able to cease their heroin use, may need referral to an inpatient supervised withdrawal program. Alternatively, an extension of the withdrawal regime over several weeks may be warranted.

Longer-term maintenance substitution treatment (with buprenorphine or methadone) should be recommended to patients who:

- cannot stop, or markedly reduce, their heroin use during the withdrawal episode;
- relapse into regular heroin use as the dose of buprenorphine is reduced or ceased;
- do not feel confident about maintaining abstinence but do not want to relapse to dependent heroin use and the associated harms.

It is recommended that such patients stabilise on a maintenance substitution medication for a longer period of time before coming off their maintenance treatment, to give them the opportunity to first distance themselves from heroin use and possibly to address any problematic psychological and social issues which may be affecting them.

4.5 Buprenorphine for heroin withdrawal in residential settings

Buprenorphine is well suited to use in inpatient withdrawal settings, given its ability to alleviate the discomfort of withdrawal symptoms without significantly prolonging their duration.

It is recommended that an interval of at least two to three days be available from the time of the last buprenorphine dose to the time of planned discharge

Duration of dosing will be determined by the length of admission available. e.g. in a 7-day admission, treatment will be limited to the first 4–5 days.

Approaches to dispensing in inpatient settings will depend on the level of supervision and staffing available. Titration regimes generally require nursing staff who can administer withdrawal scales and S8 medications, so places with limited access to nursing staff may be better suited to fixed regimes with the option of additional 'rescue' doses as required.

The additional rescue doses should only be administered :

- at least 4 hours after the earlier dose; and
- if the patient is experiencing moderate or severe withdrawal discomfort.

Buprenorphine doses in inpatient settings can generally be lower:

- outpatient regimes must accommodate higher cravings and exert blockade effects;
- outpatient regimes are generally limited to once-a-day dosing.

An evening dose (between 5pm and 10pm) is recommended, to allow relief of withdrawal symptoms until the morning. Note: buprenorphine should not be administered if there are any features of intoxication or sedation.

The following regime (Lintzeris 2002) is recommended for an admission time of approximately one week, and can be tailored accordingly:

TABLE 8: PROPOSED INPATIENT WITHDRAWAL REGIME

Day	Buprenorphine S/L tablet regime	Total daily dose
Day 1	4 mg at onset of withdrawal, & additional 2 to 4 mg evening dose prn	4 to 8 mg
Day 2	4 mg mane, with additional 2 to 4 mg evening dose prn	4 to 8 mg
Day 3	4 mg mane, with additional 2 mg evening dose prn	4 to 6 mg
Day 4	2 mg mane prn; 2 mg evening prn	0 to 4 mg
Day 5	2 mg prn	0 to 2 mg
Day 6	no dose	
Day 7	no dose	
	Total proposed dose	12 to 28 mg

This regime serves as a guide only, and considerable individual variation in withdrawal severity and medication requirements should be expected.

Post-withdrawal options should be explored prior to discharge (see next section).

- Naltrexone: Patients commencing naltrexone treatment should do so during their admission.
- Buprenorphine: Patients wishing to commence buprenorphine maintenance treatment should continue their buprenorphine as inpatients until transfer to a community-based provider can be organised.

4.6 Transition to post-withdrawal treatment

Naltrexone treatment

This section considers commencement of naltrexone after a short period of use of buprenorphine (less than 10 days) to manage withdrawal from heroin. Commencement of naltrexone after cessation of buprenorphine maintenance treatment is discussed in section 3.10. Refer to the clinical guidelines on the use of naltrexone (Bell *et al*. 2003) for treatment of opioid dependence for information on patient selection, and management once on naltrexone.

The simplest approach is to wait five to seven days after last dose of buprenorphine before commencing naltrexone. Precipitation of withdrawal by naltrexone is unlikely following a 7-day opioid-free period (Bell *et al*. 2003). However, the pharmacology of buprenorphine does enable the commencement of naltrexone earlier than this (Umbricht *et al* 1999). Naltrexone commenced early in the course of heroin withdrawal managed with buprenorphine (day 2 or 3 after cessation of heroin while buprenorphine still being prescribed) will result in increased severity of withdrawal on the day of the first dose of naltrexone, but may reduce the duration of withdrawal. This approach is best undertaken in an inpatient or intensive day-care setting that is able to respond to serious withdrawal symptoms if they occur.

A third option is to commence naltrexone 2 to 5 days after cessation of a brief course of buprenorphine for management of heroin withdrawal. This is likely to be associated with mild to moderate precipitated withdrawal. It is best undertaken in an inpatient or day care setting with the ability to respond to severe withdrawal if it were to occur.

Which procedure is best?

Administration of naltrexone within five days of stopping buprenorphine use is likely to result in opioid withdrawal following the first dose of naltrexone. This typically commences 90 minutes to 4 hours after the first naltrexone dose, peaks around 3 to 6 hours after the naltrexone dose, and generally subsides in severity within 12 to 24 hours. The withdrawal is frequently experienced as moderate to severe at its peak. Subsequent doses of naltrexone produce considerably less severe withdrawal discomfort.

Most patients undergoing this procedure request symptomatic medication, and clonidine (0.1–0.15 mg every 3 to 4 hours as required) and a benzodiazepine (e.g. diazepam 5mg, 3 to 4 hourly, maximum of 30 mg in a day, as required) should be prescribed.

Most patients find either procedure tolerable. All patients need supervision and access to the prescribing doctor.

PREPARE THE PATIENT IN ADVANCE

for the increase in withdrawal severity, the role of medications, and the risks of using heroin to overcome the withdrawal symptoms.

5 Complications or adverse events with buprenorphine treatment

5.1 Side effects

Similar to those of other opioids

The reported side-effects of buprenorphine are qualitatively similar to those of other opioids used in maintenance treatments (methadone, morphine, LAAM). An adverse drug reaction is any undesired or unintended effect of drug treatment. Adverse drug reactions may be predictable (on the basis of the drug's known actions) or unpredictable (e.g. allergic drug responses, idiosyncratic drug reactions).

Most common is opioid withdrawal

In large, multicentre trials of buprenorphine maintenance treatment, the most common adverse event (reported in over 30% of patients) has been opioid withdrawal symptoms, and these reports have been most common in patients on low doses of buprenorphine (e.g. 1 mg daily). Other commonly reported adverse events reported by the manufacturer are shown in the following table.

TABLE 9: COMMONLY REPORTED SIDE EFFECTS TO BUPRENORPHINE

Adverse event	Proportion of patients reporting adverse event	Relation to dose
Headache	8.7 %	Appears unrelated to dose
Constipation	7.5 %	More common on higher doses
Insomnia	7.3 %	Appears unrelated to dose
Asthenia	6.1 %	Appears unrelated to dose
Somnolence	4.3 %	Appears unrelated to dose
Nausea	3.5 %	More common on doses > 8 mg
Dizziness	2.7 %	More common on higher doses
Sweating	2.7 %	Appears unrelated to dose

Most are mild

In general, most adverse events to buprenorphine are mild, well tolerated, and typically occur early in treatment with symptoms subsiding over time.

Management of the side-effects, which will depend on their nature and severity, should be negotiated between patient and clinician. Conventional strategies should be adopted to manage opioid-related side effects, as indicated in the table below.

TABLE 10: COMMON SIDE EFFECTS WITH OPIOID MAINTENANCE TREATMENT

Not all of these may occur with buprenorphine

Side effect	Common causes	Things that you can do
Feeling drowsy after taking dose	• Dose too high • Other drug use (legal or illegal)	Lower the maintenance dose and review other medications the patient may be taking Review use of sedative and other drugs affecting cognition
Withdrawal symptoms maximal before next dose	• Dose too low • Changes in legal or illegal drugs that patient may be using.	Raise maintenance dose or review other drugs patient is taking
Withdrawal precipitated by buprenorphine dose	• Occurs early in treatment (or after absence from treatment) when buprenorphine dose administered soon after opioid use (e.g. heroin methadone, morphine)	Transient effect. Aim to prevent by patient education. Delay buprenorphine dose until patient experiencing opioid withdrawal Discourage use of on-top heroin.
Headache	• Common in first week of buprenorphine treatment. • Other causes of headache	Side effect is transient and generally mild. Consider aspirin or paracetamol. Consider other causes
Nausea	• Common early in treatment, particularly if buprenorphine dose too high.	Side-effect usually transient (days). Avoid rapid dose increases. Consider dose-reduction if persistent
Constipation	• All opioids do this. Will be made worse by lack of dietary fibre, fluid intake or exercise	Encourage fibre intake (fruit, cereals, vegetables), fluids, and regular exercise.
Weight gain, particularly for women	• Fluid retention caused by opioids — more likely on high doses • Eating more while in treatment; high salt intake	Lower dose Reduce fat and salt in diet, exercise regime
Poor sleep	• Dose too low and causing withdrawal at night; or	Review maintenance dose and review other medications
	• Dose too late at night, causing stimulation at time of peak effects • Other drugs (particularly stimulants in the evening, such as coffee, nicotine, amphetamines) • General anxiety or irregular sleep pattern • Depressive illness	Follow sleep hygiene recommendations.

Side effect	Common causes	Things that you can do
Amenorrhoea or oligomenorrhoea	• All opioids can do this • May be related to lifestyle stressors, poor diet, and general poor health	Periods may return after cessation of heroin use, or following withdrawal from opioids. Address other causes
Lowered sex drive	• More common with a high dose • Can be many other psychological factors (such as anxiety, poor relationship with partner etc…)	Review dose
Dental problems	• All opioids reduce saliva flow • Poor diet, dental hygiene	Encourage oral hygiene, dental floss and use of sugar free gum. Dental check-up. Reduce intake of sugary drinks and sweet food

Modified from Dunlop *et al.* (1996) Getting Through Methadone Withdrawal. Turning Point ADC: Fitzroy

5.2 Overdose

Less risk of lethal overdose: The risk of lethal overdose in an opioid-tolerant individual on buprenorphine is substantially less than that associated with the use of other opioid medications, such as methadone (Gaulier *et al* 2004; Walsh *et al* 1995). This is due to the ceiling dose response effects of buprenorphine.

Risk present with the opioid-naïve: An opioid-naïve individual may overdose with a high dose of buprenorphine. All patients should be commenced on low doses (2 to 8mg), and even lower doses (2 or 4 mg) should be considered where there is some doubt regarding the degree of neuroadaptation prior to commencing treatment.

Safer around children: The poor bioavailability of buprenorphine when taken orally reduces the risk of serious effects from accidental intake by children.

Risk increases when mixed with other sedatives: While overdose on buprenorphine is relatively uncommon, there is a greater risk when it is combined with other sedative drugs, such as alcohol, benzodiazepines, barbiturates, tricyclic antidepressants and major tranquillisers. Deaths due to the combination of buprenorphine and other sedative drugs have been reported (Faroqui *et al* 1983; Forrest 1983; Papworth 1983; Sekar & Mimpriss 1987).

High doses of antagonist needed for overdose reversal: Buprenorphine has a high affinity for μ opioid receptors, and is not easily displaced by the antagonist, naloxone. In some cases doses of 10 to 30 times the normal naloxone doses (up to 10 to 35 mg/70 kg) may be required to partially reverse the effects of buprenorphine toxicity (Eissenberg *et al* 1996; Gal 1989; Knape 1986; Quigley *et al* 1984; Rosen & Johnson 1982; Thorn *et al* 1988). However, cases have also been reported where much smaller doses (2 to 4mg) of naloxone have been effective in reversing the effects of buprenorphine (Boyd *et al* 2003).

In the event of depression of respiratory or cardiac function:

1. re-establish patient airway;
2. begin assisted or controlled ventilation with oxygen, intravenous fluids, vasopressors and other supportive measures should be employed, as indicated;
3. the long duration of action of buprenorphine should be taken into consideration when determining the length of treatment needed to reverse the effects of an overdose.

5.3 Intoxicated presentations

Intoxicated patients should not be dosed with buprenorphine, and patients should be made aware of this prior to the commencement of treatment. They may re-present later in the day (or the following day) for dosing. The prescribing doctor must be notified prior to the next dose being administered.

Patients with a history of repeated presentations for dosing while intoxicated should be reviewed by the treating doctor and the treatment plan re-considered.

5.4 Incorrect dose administered

The risks associated with an incorrect dose of buprenorphine are not as severe as with full opioid agonist medications. In the event of an incorrect dose being administered:

1. the dispensing pharmacist (or nursing staff) should immediately notify the patient and the prescriber of the error;
2. the patient should be warned of the likely consequences (increased sedation or drowsiness may occur for several hours afterwards), and warned against any additional drug use, and driving or operating machinery, for the rest of the day;
3. if a higher than intended dose has been taken the patient should be monitored for at least 6 hours by trained health professionals or in the Accident & Emergency Department of a hospital, if any of the following circumstances apply:
   a) the patient is sedated following the dose (for any reason);
   b) the patient is new to substitution treatment (within the first two weeks of maintenance treatment);
   c) a buprenorphine dose of ≥ 64mg was incorrectly administered (regardless of routine daily dose).

The patient should be reviewed by the prescribing medical officer prior to the next dose of buprenorphine. It may be that a lower dose, or no dose, is required the following day (in effect, a two-day dose has been administered).

5.5 Diversion of buprenorphine

There are no Australian data to support the suggestion that the mono and combination products differ significantly in abuse liability, and no information on how different drug-using populations will respond to the introduction of the combination product. However, following the release of the combination product in Australia, a post-marketing surveillance study will be undertaken by the National Drug and Alcohol Research Centre. This study will assess relative rates of diversion of the mono and combination products, as well as the relative efficacy of these tablets in the usual practice setting.

Reasons cited by patients for diverting buprenorphine include:

- to take sublingually at a later time;
- to inject (or snort) the medication instead of the sublingual route of administration;
- to give or sell to another person.

To minimise the risks of diversion, patients should be provided with clear guidance on how and why medication is given, and how they should present during observed consumption and be provided with the opportunity to review their treatment.

1. Patients should have their mouth cavity inspected prior to receiving their dose (gum, lollies should be removed).
2. The dose may be given in large broken pieces (to reduce potential for diversion) and dispensed into a clear plastic cup. Powdering of the drug should be avoided since it promotes both the rapid development of an easily swallowed particulate solution and the 'pasting' of the drug into the top of the gums where it might be removed from the clinic.
3. The contents of the cup should be tipped under the tongue and then the oral cavity inspected to confirm placement under the tongue.
4. Patients should be told that three to five minutes is the time required to get the most from the drug and advised not to swallow their saliva during this period as buprenorphine is not effectively absorbed if swallowed.
5. Patients should have their mouth cavity inspected after they report having absorbed the entire drug sublingually prior to leaving the dosing site.

For those caught attempting to divert their dose, it is useful to take the opportunity to discuss with the patient the reasons and thoughts behind the diversion. This may reveal misunderstandings about treatment or address concerns about their dose or well being. An explanation of how and why sublingual administration is used and the expectations of the clinic on how the patient should behave during observed supervision should be provided both verbally and in writing. The consequences of repeated diversion attempts should be explained (eg. termination from treatment, transfer to methadone). Clinics should review their dosing and observation policies and explore the layout of their dosing site, monitoring and observation methods (including where appropriate, surveillance equipment and the channelling of patients) if they find that diversion is a considerable problem.

Where there is ongoing misuse of the medication, patients should be warned that they may have to be transferred from buprenorphine treatment to methadone, which is easier to supervise, or terminated from treatment.

5.6 Investigations

Urine testing: Urine tests reveal someone's drug use in the preceding 48 to 72 hour period. A urine test for buprenorphine is an expensive investigation and should be conducted only if the results are likely to be important. Some Australian pathology laboratories do not routinely test for buprenorphine in the urine, and it will not be detected as an opioid. Please consult your pathology service to determine the availability of buprenorphine testing, and the cost.

The only possible indications for buprenorphine urine screening are to confirm whether a patient has taken the take-away doses, or to confirm that a patient is not obtaining buprenorphine from other sources.

5.7 Analgesia requirements for patients on buprenorphine

Pain may be acute or chronic, and will vary in severity. Increased doses of buprenorphine may be necessary to deal with pain. General principles of managing pain are as follows.

Acute pain

1. Where possible use simple analgesics (such as aspirin, NSAIDS, paracetamol) or tramadol. These are generally only successful/ suitable for pain of low severity.
2. Where additional opioid analgesia is required for moderate pain increasing the buprenorphine dose by 25% can have a limited effect, particularly when the dose is less than 4mg daily (limited effect above 16mg).
3. For severe pain in the hospital setting, the options for additional analgesia include:
   - regional anaesthesia if appropriate
   - ketamine infusion alone or in combination with other opiates.
4. Cessation of buprenorphine and commencement of morphine, fentanyl or similar — bearing in mind that higher than typically anticipated doses may be required. Transfer back to buprenorphine should be attempted when the pain has settled, prior to discharge from hospital. To recommence buprenorphine, first cease all other opiates, then recommence buprenorphine when early withdrawal symptoms begin to occur (usually 24 hours after the last dose of morphine). This is best conducted in consultation with a specialist addiction or acute pain service.

It has been suggested, based primarily on clinical opinion, that high doses of iv fentanyl or morphine while maintaining buprenorphine may be effective for management of severe, acute pain. However, monitoring in a high dependency unit is required because of the risk of respiratory depression (Roberts & Meyer-Witting 2005) and there is no evidence as to the effectiveness of the approach.

Patients being admitted for major surgery should advise their doctors that they are taking buprenorphine and discuss pain management options for the post operative period prior to surgery. It may be worth contacting the hospital addiction service in advance to facilitate management.

Chronic Pain

If pain cannot be managed by simple non-opioid or weak opioid analgesics, tramadol or increased doses of buprenorphine, then transfer to a stronger full agonist such as methadone should be considered.

5.8 Pregnancy and lactation

Although case reports of buprenorphine use during pregnancy have been recorded in the literature since 1995, there is not yet adequate research to definitively establish the safety, efficacy and effectiveness of buprenorphine during pregnancy and breast-feeding in humans. For this reason, pregnancy and breastfeeding are listed as contra-indications to the use of buprenorphine. This contrasts with methadone, where a significant literature has been reported over three decades. Methadone maintenance remains the first line treatment for heroin dependence in pregnancy. However, research to date has not demonstrated areas of significant concern in animal models, observational human studies or controlled studies for the use of buprenorphine in pregnancy. Over 400 cases of babies being born exposed to buprenorphine (as the mono product, ie. Subutex®) have been reported with no severe adverse events clearly linked to buprenorphine exposure. The neonatal abstinence syndrome associated with buprenorphine may be less severe and of shorter duration than that seen in methadone-exposed babies, however this has not yet been clearly established. As yet there has been little clinical experience of the effects of the combination product (Suboxone®) in pregnancy. Most experience with naloxone in pregnancy is with short-term use, e.g. in reversal of overdose. Given the lack of knowledge of the effects on the foetus of chronic exposure to naloxone during pregnancy, use of the combination product in pregnancy is not recommended.

Methadone maintenance is the first line treatment of opiate dependence in pregnancy

Buprenorphine is a Category C drug, which has implications for pregnancy.

ADEC advises that this group of drugs "has caused, or may be suspected of causing, harmful effects on the human foetus or neonate without causing malformations. These effects may be reversible." Opioid analgesics are capable of causing respiratory depression in the neonate, and withdrawal symptoms have been reported in cases of prolonged use. (NB. Methadone is also a Category C medication in pregnancy.)

Female patients seeking opiate substitution treatment who might become pregnant should be counselled on the potential risks of buprenorphine during pregnancy, with this information being reinforced and presented to them in writing.

Women wanting to become pregnant are advised to consider methadone maintenance for the management of their heroin dependence.

Substitution treatment during pregnancy

Substitution treatment is the preferred approach for the opioid dependent pregnant women due to its capacity to:

- improve access to antenatal care with improved birth outcomes;
- reduce the harmful effects of heroin and other drug use, and improve the health of pregnant women;
- reduce maternal and infant deaths associated with heroin use;
- reduce the spread of blood-borne communicable diseases associated with injecting heroin use; and
- facilitate the improvement in social functioning of the mother.

The risks of buprenorphine in pregnancy, whilst not yet accurately quantified, are unlikely given the available evidence, to be greater than the risks associated with a return to heroin use.

In studies where a comparison with methadone exists, the incidence of severe adverse events of using buprenorphine in pregnancy is less than 1 in 66.

The key issue for women who want to remain on buprenorphine during pregnancy or breastfeeding is that they understand that the safety and effectiveness of buprenorphine has not yet been fully evaluated

Withdrawal during pregnancy

For some women pregnancy is a significant motivating factor to attempt abstinence. Withdrawal from heroin is not recommended in the first or third trimesters due to possible increased risks of spontaneous abortion or premature delivery, respectively.

The patient who becomes pregnant while on buprenorphine treatment

The risks and benefits of transfer to methadone or continued buprenorphine maintenance should be discussed with all patients. There are risks of destabilisation of treatment when a woman already stable on buprenorphine is transferred to methadone. Admission to hospital should be considered for transfer to methadone, allowing for close observation of both mother and foetus, for evidence of withdrawal or distress.

The crucial issue is that pregnant women who want to continue buprenorphine treatment are aware of the lack of certainty on the safety and effectiveness of the medication. The prescribing doctor should discuss the risks and benefits of continuing buprenorphine and allow pregnant women an adequate opportunity to consider the issues of remaining on buprenorphine or transferring to methadone.

There may be situations where it is preferable for the woman to remain on buprenorphine. Given the lack of evidence and current contraindication for use of buprenorphine in pregnancy, it is desirable in these cases to consult with addiction medicine and/or specialist obstetric and paediatric units. This process should be documented (a suggested consent sheet is attached as Appendix 4)

The pregnant heroin user not in treatment

Heroin-dependent women who become pregnant should be advised to commence maintenance substitution treatment, with methadone being the preferred option. However, as stated above, the risks from using buprenorphine in pregnancy, are unlikely to be greater than the risks associated with ongoing regular heroin use, given the available evidence. If a pregnant heroin dependent woman presents wanting buprenorphine and refusing methadone, consultation with an addiction medicine specialist and/or specialist obstetric and paediatric unit is recommended.

Neonatal monitoring

Neonates of women exposed to buprenorphine should be monitored for neonatal abstinence syndrome or any other adverse events. This group of children should be followed up by paediatricians with experience in caring for children exposed in utero to drugs of dependence. Long-term follow-up (e.g. 12 to 24 months) will be required to monitor for developmental abnormalities.

Breast-feeding

It is known that only small amounts of buprenorphine and buprenorphine–naloxone pass into breast milk. Given that the infant swallows the milk, absorption of buprenorphine from breast milk would be expected to be minimal. However, there is a lack of research evidence regarding the safety and effects on development of breast fed babies exposed to buprenorphine. In the absence of adequate information of the effects of buprenorphine and buprenorphine/naloxone on breastfeeding infants, breastfeeding should be approached with some caution. However, the potential risks of buprenorphine should be balanced with the overall positive effects of breastfeeding. Consultation with a specialist paediatric unit with substance use expertise is advised.

6 Prescribing and dispensing buprenorphine

Both preparations of buprenorphine are registered as S8 medications. Special precautions should be taken by clinicians in the prescribing, handling, dispensing and storage of these medications. Specific requirements may apply in your jurisdiction — contact the relevant authority for advice (see Appendix 2).

6.1 Prescribing requirements

Jurisdictional policy should be consulted for specific requirements, but in general, prescribers should specify the following:

- the name and address of the prescribing doctor who has been authorised to prescribe;
- the patient's name and address;
- the date of the prescription;
- the preparation to be dispensed (buprenorphine or buprenorphine/naloxone sublingual tablets);
- the dose of buprenorphine to be dispensed in mg (words and numbers);
- different dose schedules must be written separately (ie 24-hour doses, 2-day or 3-day doses);
- the beginning and end dates of the prescription.

It is also good practice to include the name of the dispensing pharmacy.

6.2 Protocols for administering buprenorphine

Procedures prior to dosing

Health professionals authorised to administer buprenorphine include a pharmacist, a medical practitioner or registered nurses.

Prior to administering the medication, staff must:

- establish the identity of the patient;
- confirm that the patient is not intoxicated;
- check dose and currency of the prescription — a patient cannot be dosed if a prescription is not current;
- check that the current day is a dose day on the patient's regime;
- confirm the dose for the current day if it is an alternate-day or three-times-a-week regime.

Dispensing of the dose should be recorded in accordance with jurisdicational requirements.

Administering buprenorphine

After recording dose details in the necessary Drug of Addiction recording system, the following procedures should be observed.

1. Count and check the buprenorphine tablets into a transparent, dry dosing cup. Double check number and strength.
2. For patients unfamiliar with buprenorphine dosing, issue the following instructions:
   - place the tablets under your tongue;
   - do not chew the tablets;
   - do not swallow saliva until the tablets have dissolved (3 to 5 minutes on average);
   - do not swallow the tablets (buprenorphine tablets have poor bioavailability when taken orally compared to sublingually);
   - once the tablets are given to you they are your responsibility and will not be replaced.
3. Inspect the patient's mouth cavity — gum, lollies etc should be removed.
4. Give the cup to the patient and ask the patient to tip the contents under the tongue. Discourage patients from handling tablets.
5. Observe the patient until you are satisfied tablets are not able to be diverted (usually > 2 minutes). Ask to see "how the tablets are dissolving" enough times for this to become an acceptable part of the patient's pick up routine.
6. Patients should sign that they have received their dose. Offer cordial or water to rinse taste out of mouth.
7. The prescriber should be notified if the pharmacist has concerns that patients may be attempting to divert their medication (see Section 5.5).

Increasing the amount of time that the medication is in contact with the oral mucosa will maximise the absorption of buprenorphine. Whole tablets will promote the most gradual absorption but may be more easily diverted. Where diversion is a concern, breaking tablets into four or five pieces is recommended. Crushing buprenorphine tablets to a powder should be avoided since a particulate solution is rapidly formed which is difficult to keep under the tongue and promotes swallowing of unabsorbed medication. Strategies to promote saliva flow can help with absorption.

A1 Medications metabolised by Cytochrome P450 3A4

This information is based on the listing at http://medicine.iupui.edu/flockhart/table.htm

Inhibitors (potentially increasing blood levels of buprenorphine)

HIV antivirals

Delaviridine
Indinavir
Nelfinavir
Ritonavir

Other:

Amiodarone
Cimetidine
Clarithromycin
Erythromycin
Fluconazole
Fluvoxamine
Grapefruit juice
Itraconazole
Ketoconazole
Nefazodone
Norfloxacin
Verapamil

Substrates

Macrolide antibiotics:

Clarithromycin
Erythromycin

Anti-arrhythmics:

Quinidine

Benzodiazepines:

Alprazolam
Diazepam
Midazolam

Immune modulators:

Cyclosporine
Tacrolimus

HIV antivirals:

Indinavir
Nelfinavir
Ritonavir
Saquinavir

Prokinetic:

Cisapride

Antihistamines:

Astemizole

Calcium channel blockers:

Amlodipine
Diltiazem
Felodipine
Nifedipine
Verapamil

HMG CoA reductase inhibitors:

Atorvastatin
Cerivastatin
Lovastatin
NOT pravastatin
Simvastatin

Steroids:

Estradiol
Hydrocortisone
Progesterone
Testosterone

Miscellaneous:

Buspirone
Dapsone
Fentanyl
LAAM
Methadone
Ondansetron
Propranolol
Quinine
Tamoxifen
Trazodone
Zolpidem

Inducers (potentially decreasing blood levels of buprenorphine)

HIV antivirals:

Efavirenz
Nevirapine

Other

Barbiturates
Carbamazepine
Glucocorticoids
Modafinil
Phenobarbital
Phenytoin
Rifampin
St John's wort

A2 Consultancy and support mechanisms

Australian Capital Territory

ACT Health

GPO Box 825, Canberra ACT 2601

ACT Health — Alcohol and Drug Program

Director
Phone: (02) 6205 0947
Fax: (02) 6285 2780

Medical Officers
Phone: (02) 6244 2591
Fax: (02) 6285 2780

Chief Pharmacist
Phone: (02) 6205 0959
Fax: (02) 6285 2780

ACT Health — Policy Division

Manager, Alcohol and Other Drug Unit
Phone: (02) 6205 0909
Fax: (02) 6205 0866

ACT Health — Population Health Division

Chief Health Officer
Phone: (02) 6205 0883
Fax: (02) 6205 1884

Applications for approval to dispense buprenorphine

Health Protection Services
Pharmaceutical Services Section
Phone: (02) 6207 3974
Fax: (02) 6205 0997

Applications for approval to prescribe buprenorphine

Chief Health Officer
Phone: (02) 6205 0998
Fax: (02) 6205 0997

New South Wales

Alcohol and Drug Information Service

Phone: (02) 9361 2111
Toll Free: 1800 023 599

NSW Drug and Alcohol Specialist Advisory Service

Phone: (02) 9557 2905
Toll Free: 1800 023 687

NSW Health Centre for Drugs and Alcohol

Phone: (02) 9391 9244

Applications for authorisation to prescribe, and approval to dispense, buprenorphine and methadone

NSW Health Pharmaceutical Services Branch
PO Box 103
GLADESVILLE NSW 1675
Phone: (02) 9879 5246
Fax: (02) 9859 5170

Northern Territory

Alcohol and Other Drug Information Service (ADIS, NT)

Toll free 1800 131 350

Drug and Alcohol Clinical Advisory Service (DACAS)

Toll free 1800 111 092

Alcohol and Other Drugs Program, Policy and Program Development

Phone: (08) 8999 2691

Alcohol and Other Drugs Service, Darwin

Phone: (08) 8922 8399

Alcohol and Other Drugs Service, Central Australia

Phone: (08) 8951 7580

Applications for approval to prescribe and dispense buprenorphine

Chief Poisons Inspector
Poisons Control Branch
Department of Health and Community Services
PO Box 40596
CASUARINA NT 0811
Phone: (08) 8999 2631
Fax: (08) 8999 2420

Queensland

Policy and Specific State Information

Senior Advisor Illicit Drugs
Alcohol, Tobacco and Other Drug Branch
Phone: (07) 3234 1700
Fax: (07) 3234 1699

Medical Advisor
Alcohol, Tobacco and Other Drug Branch
Phone: (07) 3234 0957
Fax: (07) 3234 1699

Applications for approval to prescribe and dispense buprenorphine

Chief Executive
Queensland Health
Locked Bag 32
COORPAROO QLD 4151
Phone: (07) 3896 3900
Fax: (07) 3896 3933

Alcohol and Drug Information Service (ADIS)

GPO Box 8161
Brisbane Qld 4001
Phone: (07) 3837 5989
Fax: (07) 3837 5914
Free call 1800 177 833 outside Brisbane

Tasmania

Alcohol and Drug Service State Office

State Manager
Phone: (03) 6216 4260

Coordinator Illicit Drugs
Phone: (03) 6216 4262

Deputy Chief Pharmacist
Phone: (03) 6233 3906

Alcohol and Drug Service

Southern Regional Office
Manager
Phone: (03) 6230 7903

Opiate Treatment Medical Officer
Phone: (03) 6230 7903

Pharmacist
Phone: (03) 6230 7903

North/North West Regional Office
Manager
Phone: (03) 6336 5577

Opiate Treatment Medical Officer
Phone: (03) 6336 5577

Applications for approval to dispense buprenorphine

Opioid Pharmacotherapy Accreditation and Training Committee
C/o Alcohol and Drug Service
Department of Health and Human Services
PO Box 125
HOBART TAS 7001
Phone: (03) 6216 4262
Fax: (03) 6216 4267

Applications for approval to prescribe buprenorphine

Pharmaceutical Services
Department of Health and Human Services
PO Box 125
HOBART TAS 7001
Phone: (03) 6233 2064
Fax: (03) 6233 3904

South Australia

ADIS (Alcohol and Drug Information Service)

Toll Free: 1300 13 13 40

Drug and Alcohol Clinical Advisory Service

Toll Free: 1300 13 13 40

Warinilla Clinic

92 Osmond Terrace
Norwood SA 5067
Phone: (08) 8130 7500

Northern Methadone Service

22 Langford Drive
Elizabeth SA 5112
Phone: (08) 8252 4040

Southern Clinic

82 Beach Road
Christies Beach SA 5165
Phone: (08) 8326 6644

Applications for approval to prescribe and dispense buprenorphine

Drugs of Dependence Unit
Drug Strategy and Programs Branch
PO Box 6
RUNDLE MALL SA 5000
Phone: 1300 652 584
Fax: 1300 658 447

Victoria

Victorian Drug and Alcohol Clinical Advisory Service

Metro: (03) 9416 3611
Toll Free: 1800 81 2804

Direct Line

Provides counseling, information and referral
Toll Free: 1800 888 236

Youth Substance Abuse Service

Provides information, outreach and residential services for young people aged between 12 and 21 experiencing significant problems related to their use of drugs and/or alcohol.
Phone: (03) 9415 8881
Fax: (03) 9415 8882
Website: http://www.ysas.org.au

YSASLine

Provides 24 hour access to information, telephone counseling, and referral to YSAS outreach teams.

Metro: (03) 9418 1020
Toll Free: 1800 014 446

Specialist Methadone Services

Consultative service to methadone prescribers seeking expert opinion about the management of patients with special problems.

Turning Point Drug and Alcohol Centre
54 Gertrude St., FITZROY 3065
Administration
Phone: (03) 8413 8413
Fax: (03) 9416 3420

Clinical Services

Phone: (03) 8413 8444
Fax: (03) 9486 9766
Website http://www.turningpoint.org.au

Southcity Clinic

6–69 Brighton Rd., ELWOOD 3184
Phone: (03) 9525 7399
Fax:(03) 9525 7369
Website http://www.southcityclinic.com.au

Western Hospital Drug and Alcohol Service

3–7 Eleanor St, FOOTSCRAY 3011
Phone: (03) 8345 6682
Fax: (03) 8345 6027

Austin and Repatriation Medical Centre Specialist Methadone Service

Studley Rd, HEIDELBERG 3084
Phone: (03) 9496 5999 or 9496 5000

Pharmacy
Phone: (03) 9496 4999
Fax: (03) 9459 4546

Eastern Region Specialist Methadone Service

Whithorse Community Health Service
65 Carrington Street, BOX HILL, 3128
Phone: (03) 8843 2225
Fax: (03) 9898 8010

Royal Women's Hospital Chemical Dependency Unit

For women who are pregnant and use drugs.
264 Cardigan Street Carlton 3053
Phone: (03) 9344 3631

Hepatitis C Helpline

Toll Free: 1800 800 241
TTY: 1800 032 665
Vietnamese Line: 1800 456 007

AIDSLINE

Phone: (03) 9347 6099
Toll Free: 1800 133 392
TTY: 1800 032 665

Melbourne Sexual Health Centre

580 Swanston Street, Carlton 3053
Phone: (03) 9347 0244
Toll Free: 1800 032 017

Needle and Syringe Exchange Programs (NSEPs)

For contact details of Victorian NSEPs see:
http://hna.ffh.vic.gov.au/phb/9808109/index.htm
or call Direct Line (see above)

Applications for approval to prescribe and dispense buprenorphine

Drugs and Poisons Unit
Department of Human Services
GPO Box 4057
MELBOURNE VIC 3001
Phone: 1300 364 545
Fax: 1300 360 830

Western Australia

Alcohol and Drug Information Service (Public)

Phone: (08) 9442 5000
Toll Free: 1800 198 024

Clinical Advisory Service (Health Professionals)

Phone: (08) 9442 5042
Toll Free: 1800 688 847

Applications for approval to prescribe buprenorphine

Phone: (08) 9370 0307
Fax: (08) 9471 0444

Applications for approval to dispense buprenorphine

Pharmaceutical Services Branch
Department of Health
PO Box 8172
Perth Business Centre WA 6849
Phone: (08) 9388 4980
Fax: (08) 9388 4988

A3 Scales for assessing opioid withdrawal

The Subjective and Objective Opiate Withdrawal Scales assess the severity of withdrawal at the time the scale is administered. These scales can be administered multiple times in any day. The Short Opiate Withdrawal Scale is often abbreviated in literature to SOWS, but referred to here as ShOWS to avoid confusion with the Subjective Opiate Withdrawal Scale. This scale assesses the patient's experience of withdrawal in the preced ing 24 hours. As such the ShOWS is only valid for once daily administration. It includes assessment of sleep disturbance which is an aspect of withdrawal that is significant to patients.The Clinical Opiate Withdrawal Scale (COWS) is the newest of the scales. It combines objective and subjective items. Like the SOWS and OOWS it can be administered multiple times in a day. It has the advantage of being quick to administer.

The Subjective Opiate Withdrawal Scale (SOWS)

(Handelsman *et al* 1987)

Date . . . . . Time . . . . . .

Please score each of the 16 items below according to how you feel NOW (circle one number)						
	Symptom	**not at all**	**a little**	**moderately**	**quite a bit**	**extremely**
1	I feel anxious	0	1	2	3	4
2	I feel like yawning	0	1	2	3	4
3	I am perspiring	0	1	2	3	4
4	My eyes are teary	0	1	2	3	4
5	My nose is running	0	1	2	3	4
6	I have goosebumps	0	1	2	3	4
7	I am shaking	0	1	2	3	4
8	I have hot flushes	0	1	2	3	4
9	I have cold flushes	0	1	2	3	4
10	My bones and muscles ache	0	1	2	3	4
11	I feel restless	0	1	2	3	4
12	I feel nauseous	0	1	2	3	4
13	I feel like vomiting	0	1	2	3	4
14	My muscles twitch	0	1	2	3	4
15	I have stomach cramps	0	1	2	3	4
16	I feel like using now	0	1	2	3	4

Total score range 0–64.

Objective Opioid Withdrawal Scale (OOWS)

(Handelsman *et al* 1987)

Date . . . . . Time . . . . . .

Observe the patient during a 5 minute observation period then indicate a score for each of the opioid withdrawal signs listed below (items 1–13). Add the scores for each item to obtain the total score

	Sign	Measures		Score
1	Yawning	0 = no yawns	1 = ≥ 1 yawn	
2	Rhinorrhoea	0 = < 3 sniffs	1 = ≥ 3 sniffs	
3	Piloerection (observe arm)	0 = absent	1 = present	
4	Perspiration	0 = absent	1 = present	
5	Lacrimation	0 = absent	1 = present	
6	Tremor (hands)	0 = absent	1 = present	
7	Mydriasis	0 = absent	1 = ≥ 3 mm	
8	Hot and Cold flushes	0 = absent	1 = shivering / huddling for warmth	
9	Restlessness	0 = absent	1 = frequent shifts of position	
10	Vomiting	0 = absent	1 = present	
11	Muscle twitches	0 = absent	1 = present	
12	Abdominal cramps	0 = absent	1 = Holding stomach	
13	Anxiety	0 = absent	1 = mild – severe	
	TOTAL SCORE			

Total score range 0–13

The Short Opiate Withdrawal Scale (ShOWS)

(Gossop 1990)

Please put a check mark in the appropriate box if you have suffered from any of the following conditions in the last 24 hours:

	None	Mild	Moderate	Severe
Feeling sick				
Stomach cramps				
Muscle spasms/twitching				
Feelings of coldness				
Heart pounding				
Muscular tension				
Aches and pains				
Yawning				
Runny eyes				
Insomnia/problems sleeping				

Scoring: None = 0
Mild = 1
Moderate = 2
Severe = 3

Clinical Opiate Withdrawal Scale

(Wesson & Ling 2003)

For each item, circle the number that best describes the patient's signs or symptoms. Rate on just the apparent relationship to opiate withdrawal. For example, if heart rate is increased because the patient was jogging just prior to assessment, the increased pulse rate would not add to the score.

Patient's Name	Date and Time
Reason for this assessment	
Resting Pulse Rate . . . . . beats/minute *Measured after patient is sitting or lying for one minute* 0 pulse rate 80 or below 1 pulse rate 81–100 2 pulse rate 101–120 4 pulse rate greater than 120	**GI Upset:** *over last ½ hour* 0 no GI symptoms 1 stomach cramps 2 nausea or loose stool 3 vomiting or diarrhea 5 multiple episodes of diarrhea or vomiting
Sweating: *over past ½ hour not accounted for by room temperature or patient activity* 0 no report of chills or flushing 1 subjective report of chills or flushing 2 flushed or observable moistness on face 3 beads of sweat on brow or face 4 sweat streaming off face	**Tremor**: *observation of outstretched hands* 0 no tremor 1 tremor can be felt, but not observed 2 slight tremor observable 4 gross tremor or muscle twitching
Restlessness: *Observation during assessment* 0 able to sit still 1 reports difficulty stilling still, but is able to do so 3 frequent shifting or extraneous movements of legs/arms 5 unable to sit still for more than a few seconds	**Yawning**: *Observation during assessment* 0 no yawning 1 yawning once or twice during assessment 2 yawning three or more times during assessment 4 yawning several times/minute
Pupil size 0 pupils pinned or normal size for room light 1 pupils possibly larger than normal for room light 2 pupils moderately dilated 5 pupils so dilated that only the rim of the iris is visible	Anxiety or Irritability 0 none 1 patients reports increasing irritability or anxiousness 2 patient obviously irritable or anxious 4 patient so irritable and anxious that participation in the assessment is difficult
Bone or Joint aches: *If patient was having pain previously, only the additional component attributed to opiate withdrawal is scored* 0 not present 1 mild diffuse discomfort 2 patient reports severe diffuse aching of joints/ muscles 4 patient is rubbing joints or muscles and is unable to sit still because of discomfort	**Gooseflesh skin** 0 skin is smooth 3 piloerection of skin can be felt or hairs standing up on arms 5 prominent piloerection

Patient's Name	Date and Time
Reason for this assessment	
Runny nose or tearing: *Not accounted for by cold symptoms or allergies* 0 not present 1 nasal stuffiness or unusually moist eyes 2 nose running or tearing 4 nose constantly running or tears streaming down cheeks	Total score . . . . . . *The total score is the sum of all 11 items* Initials of person completing assessment: . . . . .

Score: 5–12 = mild; 13–24 = moderately severe; more than 36 = severe withdrawal

A4 Patient consent form for buprenorphine treatment during pregnancy/ breastfeeding

I . . . . . am currently in treatment with buprenorphine for the management of my opiate dependence, and wish to continue treatment with buprenorphine during my pregnancy / period of breastfeeding, rather than transfer to methadone.

In making this decision, I understand that:

the safety of buprenorphine during pregnancy or breastfeeding remains uncertain at this stage,

pregnancy and breastfeeding are currently listed as contraindications for the use of buprenorphine in Australia by the Therapeutic Goods Administration,

I will need to attend regularly (and as directed) for antenatal care at . . . . . Hospital,

I will need to attend regularly for appointments with my treatment team at . . . . . Hospital,

Doctor . . . . . has explained the potential risks and benefits of continuing buprenorphine during my pregnancy and afterwards.

Name: . . . . . .

Signed: . . . . . Date: / /

Witness: . . . . . Date: / /

A5 Further reading and references

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