

# **Clinical guidelines: buprenorphine treatment of heroin dependence**

Clinical guidelines and procedures for the use of buprenorphine in the treatment of heroin dependence

## **Authors**

**Lintzeris N, Clark N, Muhleisen P, Ritter A  
Ali R, Bell J, Gowing L, Hawkin L, Henry Edwards S, Mattick RP, Monheit B, Newton  
I, Quigley A, Whicker S, White J**

**Medical Editor  
Elizabeth Vorrath**

**March 2001**

## Introduction

Buprenorphine, in sublingual tablet form (Subutex®), has recently been registered in Australia for the management of opioid dependence including maintenance and detoxification, within a framework of medical, social and psychological treatment. This preparation is effective both in the long-term, as a maintenance treatment program, and in the short-term as part of a heroin withdrawal program. To assist in the safe and effective implementation of buprenorphine treatment in Australia, the following national guidelines have been commissioned by the Commonwealth Department of Health and Aged Care under the auspices of the National Expert Advisory Committee on Illicit Drugs (NEACID).

These guidelines cover both the maintenance and withdrawal programs using buprenorphine. Section 1 explains the clinical pharmacology of the preparation; Section 2 covers the commencement of buprenorphine treatment; Section 5, complications and adverse events; and Section 6 discusses prescribing and dispensing issues. In all of these sections, both maintenance and withdrawal programs are covered. In Sections 3 and 4, however, guidelines and procedures are set out separately for each program: for maintenance treatment in Section 3, and withdrawal programs in Section 4.

This set of guidelines has been developed through a consensus process by a working party of senior Australian clinicians and researchers who have experience in the use of buprenorphine in a variety of jurisdictions. The original draft of the maintenance guidelines for this project was developed as part of the Buprenorphine Implementation Trial by the Turning Point Alcohol and Drug Centre. The Clinical Guidelines for the Buprenorphine Implementation Trial were piloted by over 20 medical practitioners (both specialists and general practitioners) and 30 pharmacies involved in delivering buprenorphine maintenance treatment. In addition to the participants (patients, doctors, pharmacists and researchers) of the Buprenorphine Implementation Trial, the following individuals have contributed to the development of these clinical guidelines:

**In the USA:** Paul Fudala, Alice Huber, Ed Johnson, Surita Lao, Walter Ling, Laura McNicholas, Boris Meandzija, Charles O'Brien, Richard Rawson, Richard Schottenfeld, George Woody. **In France:** Marc Auricombe **In the UK:** Fergus Law, Judith Myles, David Nutt, Chris Chapleo, Don Walter. **And in Australia:** Louise Rushworth, Reckitt Benkizer; Gabriele Bammer, National Centre for Population Health and Epidemiology; Adrian Dunlop, Nadine Ezard, Alan Gisbjers, Sandra Hocking, Jozica Kutin, Paul Murray, and Greg Whelan.

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

The contribution of Ms Elizabeth Vorrath, Medical Editor, in ensuring that the guidelines are clear and easy to read is gratefully acknowledged.

## TABLE OF CONTENTS

<b>SECTION 1. CLINICAL PHARMACOLOGY .....</b>	<b>4</b>
<i>General Information.....</i>	<i>4</i>
<i>Withdrawal syndrome from buprenorphine .....</i>	<i>5</i>
<i>Safety and side effects .....</i>	<i>6</i>
<i>Drug Interactions.....</i>	<i>7</i>
<i>SUMMARY OF THE PHARMACOLOGICAL AND CLINICAL PROPERTIES OF     BUPRENORPHINE .....</i>	<i>8</i>
<b>SECTION 2. ENTRY INTO BUPRENORPHINE TREATMENT .....</b>	<b>9</b>
2.1 SUITABILITY FOR TREATMENT WITH BUPRENORPHINE.....	9
<i>Indications.....</i>	<i>9</i>
<i>Contraindications.....</i>	<i>10</i>
<i>Precautions .....</i>	<i>10</i>
2.2 ASSESSMENT PROCEDURES.....	12
2.3 INFORMED CONSENT AND PATIENT LITERATURE.....	13
2.4 PERMITS AND REGISTRATION OF PATIENTS.....	14
<b>SECTION 3. GUIDELINES FOR MAINTENANCE TREATMENT.....</b>	<b>15</b>
3.1 SELECTING MAINTENANCE PHARMACOTHERAPIES .....	15
3.2 INDUCTION TO BUPRENORPHINE TREATMENT .....	16
<i>Commencing buprenorphine from heroin use.....</i>	<i>16</i>
<i>Transferring from methadone maintenance treatment.....</i>	<i>17</i>
3.3 STABILISATION .....	21
<i>Regular and high risk use of heroin.....</i>	<i>24</i>
3.4 MAINTENANCE DOSING.....	24
<i>Dose levels .....</i>	<i>24</i>
<i>Frequency of dosing: alternate-day and three-times-a-week dosing regimes.....</i>	<i>24</i>
3.5 TAKE-AWAY DOSES .....	26
<i>Absence from pharmacy in patients ineligible for take-away doses .....</i>	<i>27</i>
3.6 ANCILLARY INTERVENTIONS.....	27
3.7 CONTINUED HIGH-RISK DRUG USE.....	28
3.8 MISSED DOSES .....	29
<i>Single dose missed.....</i>	<i>29</i>
<i>Multiple doses missed.....</i>	<i>29</i>
3.9 CESSATION OF BUPRENORPHINE MAINTENANCE TREATMENT.....	30
<i>Withdrawal from buprenorphine maintenance treatment .....</i>	<i>30</i>
<i>The use of buprenorphine to assist withdrawal from methadone maintenance programs.....</i>	<i>32</i>
<i>Commencing naltrexone following buprenorphine maintenance treatment .....</i>	<i>32</i>
<i>Transferring to methadone.....</i>	<i>33</i>
<b>SECTION 4. GUIDELINES FOR THE MANAGEMENT OF HEROIN WITHDRAWAL .....</b>	<b>35</b>
4.1 HEROIN WITHDRAWAL IN CONTEXT .....	35
<i>Heroin withdrawal defined.....</i>	<i>35</i>

<i>Objectives of withdrawal services</i> .....	35
4.2 NON-PHARMACOLOGICAL ASPECTS IN MANAGING HEROIN WITHDRAWAL.....	37
<i>Treatment selection</i> .....	37
<i>Supportive care</i> .....	39
<i>Monitoring</i> .....	40
4.3 OVERVIEW OF BUPRENORPHINE IN THE MANAGEMENT OF HEROIN WITHDRAWAL.....	41
<i>Efficacy of buprenorphine compared to other withdrawal medication regimes (literature review)</i> .....	41
<i>The role of buprenorphine in withdrawal</i> .....	41
<i>Preventing precipitated withdrawal on commencing buprenorphine</i> .....	42
<i>Use of ancillary medications in conjunction with buprenorphine</i> .....	42
<i>Continued use of heroin and other drugs</i> .....	43
<i>Gateway model of treatment with buprenorphine</i> .....	43
4.4 BUPRENORPHINE REGIMENS IN OUTPATIENT WITHDRAWAL SETTINGS.....	44
4.5 BUPRENORPHINE FOR HEROIN WITHDRAWAL IN RESIDENTIAL SETTINGS .....	46
4.6 TRANSITION TO POST-WITHDRAWAL TREATMENT .....	48
<i>Transition to maintenance treatment</i> .....	48
<i>Commencing naltrexone treatment after short duration buprenorphine withdrawal</i> .....	48
<b>SECTION 5 . COMPLICATIONS OR ADVERSE EVENTS WITH BUPRENORPHINE</b>	
<b>TREATMENT.....</b>	<b>51</b>
5.1 SIDE EFFECTS .....	51
5.2 OVERDOSE.....	53
5.3 INTOXICATED PRESENTATIONS.....	53
5.4 INCORRECT DOSE ADMINISTERED .....	54
5.5 DIVERSION OF BUPRENORPHINE.....	54
5.6 INVESTIGATIONS .....	55
5.7 ANALGESIA REQUIREMENTS FOR PATIENTS ON BUPRENORPHINE.....	55
5.8 PREGNANCY AND LACTATION .....	56
<b>SECTION 6. WRITING PRESCRIPTIONS &amp; DISPENSING BUPRENORPHINE.....</b>	<b>58</b>
6.1 WRITING PRESCRIPTIONS.....	58
6.2 PROTOCOLS FOR ADMINISTERING BUPRENORPHINE.....	58
<i>Procedures prior to dosing</i> .....	58
<i>Administering buprenorphine</i> .....	59
<b>APPENDIX 1.....</b>	<b>60</b>
<b>ABBREVIATED CLINICAL GUIDELINES FOR THE USE OF BUPRENORPHINE IN THE</b>	
<b>TREATMENT OF HEROIN DEPENDENCE.....</b>	<b>60</b>
<b>APPENDIX 2.....</b>	<b>69</b>
<b>APPENDIX 3.CONSULTANCY AND SUPPORT MECHANISMS .....</b>	<b>71</b>

## SECTION 1. CLINICAL PHARMACOLOGY

### General Information

#### *What is Buprenorphine?*

Buprenorphine is a derivative of the morphine alkaloid, thebaine, and is a *partial opioid agonist* at the  $\mu$  opioid receptors in the nervous system. It is also a  $\kappa$  (kappa) opioid receptor antagonist. It has low intrinsic agonist activity, only partially activating  $\mu$  opioid receptors, thus producing a milder, less euphoric and less sedating effect than full opioid agonists such as heroin, morphine and methadone. Nevertheless, its activity is usually sufficient to diminish cravings for heroin, and prevent or alleviate opioid withdrawal in dependent heroin users. Buprenorphine also has a high affinity for  $\mu$  opioid receptors, binding more tightly to these receptors than full opioid agonists. It therefore reduces the impact of additional heroin (or other opioid) use, by preventing heroin from occupying these receptors. By its dual effects of producing opioid responses while blocking the effects of additional heroin use, buprenorphine reduces the self-administration of heroin.

#### *What form does it come in?*

The buprenorphine product registered in Australia for treating opioid dependence is Subutex®, a sublingual tablet preparation of buprenorphine hydrochloride in 0.4, 2, and 8 mg strengths. Buprenorphine is also registered in Australia for the management of short term (not more than one week) relief of moderate to severe pain, including post-operative and terminal and chronic pain as Temgesic® sublingual tablets and ampoules for intramuscular or subcutaneous injection. Sublingual buprenorphine tablets have approximately 30-35% of the bioavailability of intravenous buprenorphine preparations<sup>1</sup>. Buprenorphine undergoes extensive first pass metabolism when taken orally.

#### *How is it metabolised?*

Peak plasma concentrations are achieved 1 - 2 hours after sublingual administration. Buprenorphine has a distribution half-life of 2 - 5 hours. It is principally metabolised by two hepatic pathways: conjugation with glucuronic acid and N-de-alkylation. 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 urine.

---

<sup>1</sup> The majority of early studies using sublingual buprenorphine used a liquid solution of buprenorphine in 30% aqueous ethanol, with a bioavailability of approximately 40% of subcutaneous preparations. The commercial sublingual tablet preparation of buprenorphine (Subutex®) is reported as having 50 - 80% of the bioavailability of the ethanol solution (Shuh and Johansen 1999; Ajir *et al* 2000). In practice, sublingual tablet doses should be approximately 50% greater than sublingual solution doses referred to in earlier research studies (for example, 8 mg sublingual solution corresponds approximately to a 12 mg sublingual tablet dose).

Buprenorphine has an elimination half-life of 24 - 37 hours. It is long-acting, relative to the dose administered. Peak clinical effects occur 1 - 4 hours after sublingual administration, with continued effects for up to 12 hours at low doses (2 mg), but as long as 48 - 72 hours at higher doses (16 or 32 mg). The extended duration of action of buprenorphine is thought to relate to three factors:

- its very high affinity for opioid  $\mu$  receptors (once bound to these receptors it is dislodged only slowly);
- its high lipophilicity (low levels of buprenorphine are released slowly from fat stores, particularly with chronic dosing).
- Reabsorption of buprenorphine after intestinal hydrolysis of the conjugated metabolite.

**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. < 4 mg) 24 - 72 hours at high dose (e.g. >16 mg)

Buprenorphine also exhibits antagonist effects at the  $\kappa$  opioid receptor. The role of these receptors in humans is still poorly understood, but excess endogenous  $\kappa$  agonist activity appears to be implicated in both affective and psychotic conditions. Buprenorphine's antagonist effects at the  $\kappa$  receptor are thought to produce anti-depressant and anti-psychotic effects in some people. However, as further research is needed into these effects, buprenorphine is not currently indicated for these conditions.

### **Withdrawal syndrome from buprenorphine**

Its partial agonist properties, along with its slow dissociation from opioid receptors, are thought to explain why opioid withdrawal syndrome is milder with the cessation of buprenorphine treatment, than with heroin, morphine or methadone. Typically, the withdrawal syndrome following the abrupt cessation of long-term buprenorphine treatment emerges within 3 – 5 days of the last dose, and mild withdrawal features continue for up to several weeks. Treatment with opioid antagonists (eg naltrexone) can be commenced within days of the cessation of low-dose buprenorphine treatment without precipitating severe opioid withdrawal. This enables patients to transfer promptly to naltrexone treatment, and avoid relapse and treatment drop-out. By contrast, naltrexone is not usually started until 10 - 14 days after the cessation of methadone (Bell *et al* 1999 : *Interim National Naltrexone Guidelines*).

Withdrawal is milder and transfers to alternate treatments are more rapid

## Safety and side effects

*High doses:* Dose response studies show that, because of its ceiling effects, high doses (16 mg daily or more) do not result in substantially greater peak opioid effects than lower doses (8 or 12 mg). Doses many times greater than normal therapeutic doses appear to be well-tolerated, and rarely result in clinically-significant respiratory depression, even in non-opioid-tolerant individuals.

**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, is still unclear, with several deaths having been reported. Naloxone is of limited use in resuscitating individuals who have overdosed on high doses of buprenorphine (See section 5.2 on Management of Overdose).

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

**Not safe mixed with high doses of other sedatives**

*Side effects:* The side effects of buprenorphine are similar to those of other opioids, the most common being:

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

Many patients report less sedation on buprenorphine than on methadone. Like all opioid medications, buprenorphine may affect the capacity of patients to drive or operate machinery during the early stages of treatment or following dose increases. It appears to have minimal impact on hepatic function, although its effects in very high doses remain unclear.

**Side effects - similar to other opioids**

Under certain circumstances, buprenorphine may precipitate opioid withdrawal symptoms 1 - 4 hours after the first dose. It has a higher affinity and lower intrinsic activity than 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. 1 - 4 hours after initial administration). The phenomenon of precipitated withdrawal has particular clinical relevance during the induction of heroin users and methadone patients (see Section 3.2).

**May induce rapid opioid withdrawal**

## 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 tranquilisers. **A number of deaths have been reported involving the combination of buprenorphine with benzodiazepines and other sedatives.**
- *opioid antagonists (naloxone and naltrexone)*. Buprenorphine has higher affinity for  $\mu$  opioid receptors than the opioid antagonists. In the event of overdose of buprenorphine, very high doses of naloxone are required to reverse its effects (10-35 mg have been reported). Naltrexone can precipitate a delayed withdrawal reaction in patients on buprenorphine.
- *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. The initial dose of buprenorphine can precipitate opioid withdrawal in patients with high levels of neuroadaptation to full opioid agonists.
- *hepatic enzyme inducers and inhibitors*. Buprenorphine is metabolized by the hepatic microsomal enzyme system (CYP 3A4). While current evidence is inconclusive, it is thought that the concurrent use of medications which induce or inhibit microsomal enzyme activity will have minimal clinical impact on buprenorphine dosing requirements.

TABLE 2

**SUMMARY OF THE PHARMACOLOGICAL AND CLINICAL PROPERTIES  
OF BUPRENORPHINE**

<i>Property</i>	<i>Clinical implication</i>
Produces opioid effects	Reduces cravings for heroin and enhances treatment retention. Less sedating than full agonists (heroin, morphine or methadone).
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 other opioids (e.g. morphine).
Long duration of action	Allows for once-a-day to three-times-a-week dosing schedules.
Ceiling on dose response effect	Higher doses (e.g. >16 mg) may not increase the opioid agonist effects, while prolonging 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.
No severe withdrawal precipitated by opioid antagonists.	Treatment with naltrexone can be commenced within days of buprenorphine. May complicate management of heroin overdose requiring high naloxone doses.
Side effect profile similar to other opioids	Generally well tolerated, with most side effects transient.

## SECTION 2. ENTRY INTO BUPRENORPHINE TREATMENT

### 2.1 Suitability for treatment with buprenorphine

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

#### Indications

##### 1. Buprenorphine treatment is only indicated for those who are opioid-dependent.

What is opioid dependence?

---

#### 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.
- *Consciousness of damage being out of control*: 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.

---

#### NEUROADAPTATION TO OPIOIDS

Evidence of neuroadaptation (or physical dependence):

1. tolerance of the opioid;
2. onset of withdrawal syndrome on stopping or decreasing use.

**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.

**2. The patient must be at least 18 years of age.** The prescribing doctor should seek a second or specialist opinion before treating anyone under 18 years of age. (Note: While buprenorphine has been registered for administration to people aged 16 and over caution should be exercised in prescribing a drug of dependence for anyone in the 16-17 age group.)

**3. The patient must be able to provide proof of identity - a requirement for treatment with any S8 medication.**

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

<p style="text-align: center;"><b><u>Suitability for Buprenorphine Treatment</u></b> <b>opioid-dependent</b> <b>18 years or older</b> <b>proof of identity</b> <b>capable of informed consent</b></p>
---

### **Contraindications**

1. Anyone with known hypersensitivity and/or severe side-effects from previous exposure to buprenorphine is ineligible for buprenorphine treatment.
2. Pregnant women and nursing mothers are also ineligible at this stage, as there is insufficient evidence that it is safe for either the developing fetus or the breast-fed neonate, and there is evidence in other species of harms. Developmental toxicity studies of buprenorphine in pregnant rats and rabbits have shown fetotoxicity, including post-implantation loss, and decreased post-natal survival with no evidence of teratogenicity. The described effects occurred at systemic exposures similar to the maximum anticipated human dose of 32 mg/day.. In addition, maternal oral administration at high doses (80 mg/kg/day) during gestation and lactation resulted in a slight delay in the development of some neurological functions (surface righting reflex and startle response) in neonatal rats. In humans, there is currently not sufficient data to evaluate potential teratogenic or fetotoxic effects of buprenorphine in pregnancy. However, high doses, even for short durations, may induce respiratory depression in neonates. During the last three months of pregnancy, chronic use of buprenorphine may be responsible for a withdrawal syndrome in neonates.

Animal studies indicate buprenorphine has the potential to inhibit lactation. Buprenorphine passes into the mother's milk, therefore breast-feeding while using buprenorphine is contra-indicated until its safety has been fully established.

3. Severe respiratory or hepatic insufficiency.

### **Precautions**

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

1. *High-risk polydrug use.* All opioid substitution treatments should be approached with caution in individuals using other drugs, particularly sedative drugs such as alcohol, benzodiazepines 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 chronic obstructive airways disease or cor pulmonale, and in individuals with a substantially decreased respiratory reserve, pre-existing respiratory depression, hypoxia, or hypercapnea. **In such patients, even normally safe therapeutic doses of opioids may decrease respiratory drive whilst simultaneously increasing airways resistance to the point of apnoea.**
- *Acute abdominal conditions.*
- *Severe hepatic disease.* Caution needs to be taken in considering buprenorphine treatment for people with clinically significant hepatic failure. 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.
- *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;
  - pre-existing diabetes mellitus or a pre-disposition to it, with the possibility of increases in serum glucose on buprenorphine;
  - 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 acute psychosis, severe depression, or other psychiatric conditions which severely compromise the capacity to give informed consent. 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 (although it is not registered for this purpose), but at much lower doses than for heroin dependence. Ideally, chronic pain is best managed under the supervision of a specialist multidisciplinary team, and appropriate referral or consultation should be considered.

5. *Transfer from methadone maintenance.* Buprenorphine may cause difficulties in transferring from methadone by precipitating withdrawal (see Section 3.2). This is most

likely to occur in patients on high doses of methadone, and attempts to reduce the methadone dose to below 60 mg (and preferably below 40 mg) should be made before initiating buprenorphine. **Methadone patients who relapse into regular heroin use following the reduction of their methadone dose are likely to find transition to buprenorphine difficult, if not unachievable.**

#### **EXERCISE CAUTION**

With patients in any of the following categories

**high-risk polydrug use**  
**concomitant medical conditions (see list above)**  
**concomitant psychiatric conditions**  
**suffering chronic pain**  
**transfer from methadone maintenance**

## **2.2 Assessment procedures**

A careful assessment should be conducted at the outset of buprenorphine treatment. The following issues should be addressed:

### *History*

- 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 to each drug class.
- Participation in high-risk drug behaviours, particularly overdoses, self-injury, or polydrug intoxication.
- History of prior attempts at withdrawal, maintenance and other treatment - what has worked and not worked before.
- Social circumstances, including home environment, social supports, employment, and barriers to change.
- Medical and psychiatric history, with particular attention to unstable or active conditions which might potentially complicate treatment.
- Pregnancy and contraception.
- Motivations and goals for treatment. Finding the right approach requires an understanding of the **reasons for seeking treatment** and of **patient goals and expectations**.

### *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.

#### *Investigations*

- **Urinary drug screens** can be helpful in clarifying or confirming an unclear drug use history. However, delays in getting the results of routine urine tests often limits their usefulness at initial assessment.
- **Liver function tests and 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).

A comprehensive assessment for buprenorphine treatment 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.

### **2.3 Informed Consent and Patient Literature**

**The participation of an informed patient in the clinical decision-making process is important 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 fully informed patients and their opportunity to discuss with the service provider the following topics:

- what is buprenorphine, how does it work, and what are its advantages & 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 conditions of involuntary discharge?

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.

**Buprenorphine may affect the capacity of patients to drive or operate machinery** during the early stages of treatment, after an increase in dose, or when patients are also taking other drugs. Warn patients about this effect before entry into treatment, when the dose of buprenorphine is increased, or when the use of other drugs is suspected.

## **2.4 Permits and Registration of Patients**

Buprenorphine is an S8 medication.

- **A medical practitioner must be approved by the Department of Human Services to prescribe it.**
- **A prescribing doctor must hold a permit from the Department of Human Services for each client being treated.**

**Victorian administrative arrangements (such as arrangements for your absence, prescription writing, documentation to pharmacist, interim treatment without a permit, transfers) and policy are the same as for methadone (refer to the *Methadone Guidelines for Prescribers and Pharmacists*)**

## SECTION 3. GUIDELINES FOR MAINTENANCE TREATMENT

### 3.1 Selecting maintenance pharmacotherapies

Current evidence suggests that key treatment outcomes for maintenance buprenorphine and methadone treatment are comparable under optimal treatment conditions. Whilst there is no evidence of the greater efficacy of one treatment over the other, patients or clinicians may develop personal preferences. These might reflect:

- **Response to treatment.** Ultimately, the continued use of a medication should depend on its ability to meet the aims and objectives of treatment. This requires the identification of treatment goals by the patient and the individual service provider, and decisions about how the treatment outcomes will be assessed.

**Where these 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 a 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 high doses of an agonist treatment (methadone).
- **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.
  - **Logistics of participating in treatment,** including issues such as ease of access for participants, frequency of dispensing, convenient location of treatment services and the costs to patients, service providers and funding bodies. Once stabilised on a daily dosing regime, the majority of patients on buprenorphine will be able to switch to an alternate-day, or three-times-a-week dosing regime. This should be more convenient for patients and reduce the need for regular take-away doses. Not all patients will be comfortable on alternate-day buprenorphine dosing, and may require daily doses.
  - **Ease of withdrawal from maintenance buprenorphine treatment.** A limiting factor for many patients considering maintenance treatment is the problem of dependence on the maintenance opioid. As it is only a partial agonist and dissociates slowly from receptors,

buprenorphine appears to have a milder withdrawal syndrome than methadone. Nevertheless, current research indicates that relapse rates to heroin use are comparable for patients discontinuing maintenance treatment from either opioid.

- **Patient (and clinician) expectancy.** Expectations of any medication may impact seriously on its perceived outcomes. The introduction of new pharmacotherapies for heroin dependence may give rise to unrealistic expectations in patients, their families, and even service providers.
- **Capacity for transfer from methadone maintenance.** Some patients require high doses of methadone to stabilise their heroin use, and a marked reduction can cause a relapse to regular heroin use. For patients who cannot reduce below high doses of methadone (i.e. 60 mg) without becoming destabilised, transfer to buprenorphine should not be recommended unless it is part of a broader plan of gradual withdrawal from maintenance substitution treatment.

**FACTORS TO CONSIDER WHEN SELECTING MAINTENANCE  
PHARMACOTHERAPIES**

Response to treatment

Individual variation in absorption, metabolism & clearance rates

Adverse effects

Logistics of participating in treatments

Ease of withdrawal from maintenance buprenorphine treatment

General expectations of the treatment

Capacity for transfer from methadone maintenance

### 3.2 Induction to buprenorphine treatment

#### Commencing buprenorphine from heroin use

**The initial dose of buprenorphine should be between 2 and 8 mg.  
The initial dose should not be greater than 8mg.**

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

- **Degree of neuroadaptation to opioids.** Patients with a low degree of neuroadaptation to opioids (low opioid tolerance) should be commenced on a dose of 2 or 4 mg. In instances where the doctor is uncertain of the degree of neuroadaptation, the patient should be

commenced on a dose of 4 mg. Patients with high levels of neuroadaptation should commence on 6 or 8 mg.

- **Extent of heroin withdrawal at the time of first buprenorphine dose.** Patients experiencing considerable opioid withdrawal at the time of the first dose require higher doses of buprenorphine to alleviate withdrawal symptoms. Patients with little or no indication of opioid withdrawal at the time of the first dose should be prescribed a lower dose, or be asked to re-present at a later time (see rationale below).
- **The perceived likelihood of concurrent drug abuse**, including alcohol consumption, unauthorised 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 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 “**Precautions**”).

<p style="text-align: center;"><b>The first dose of buprenorphine should be administered at least 6 hours after last heroin use.</b></p>
--

Care should be taken by prescribing doctors, pharmacists and nursing staff, not to administer the first dose to a patient within 6 hours of heroin use, and especially not to patients intoxicated on opioids. If they do, the patient may experience opioid withdrawal, as the buprenorphine displaces heroin from the opioid receptors. Buprenorphine-precipitated withdrawal typically begins 1- 4 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.

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 6 hours prior to the next dose of buprenorphine.

### **Transferring from methadone maintenance treatment**

Buprenorphine has a higher affinity for  $\mu$  opioid receptors than methadone, but a weaker action (lower intrinsic activity) at these receptors. When methadone patients take a dose of buprenorphine, the methadone is displaced from the  $\mu$  opioid receptors by buprenorphine. Patients on low doses of methadone (e.g. less than 30 mg) generally tolerate this transition with minimal discomfort. **However, patients on higher doses of methadone may find the**

## replacement of methadone with buprenorphine precipitates transient opioid withdrawal.

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 low dose prior to transferring to buprenorphine, in order to minimise any opioid withdrawal features. The following table describes key factors in the development of precipitated withdrawal.

TABLE 3  
KEY FACTORS AFFECTING PRECIPITATED WITHDRAWAL

Factor	Discussion	Recommended strategy
Dose of methadone	Doses greater than 30 mg of methadone are more often associated with precipitated withdrawal. In general, the higher the methadone dose, the more severe the withdrawal experienced.	Attempt transfer from low dose of methadone (e.g. < 40 mg where possible). Patients on > 60 mg methadone should not attempt transfer.
Time between last methadone dose and first buprenorphine dose	Buprenorphine should not be taken within 24 hours of last methadone dose. Increasing the interval between last dose of methadone and first dose of buprenorphine reduces the incidence and severity of precipitated withdrawal.	Cease methadone and delay first dose of buprenorphine until patient is experiencing features of methadone withdrawal
Dose of buprenorphine	Very low doses of buprenorphine (e.g. 2 mg) are generally inadequate to substitute for methadone (unless the methadone dose is very low). High first doses of buprenorphine (e.g. 8 mg or more) are more likely to precipitate withdrawal, as there is greater displacement of methadone from the receptors. <i>This is a common mistake by inexperienced prescribers.</i>	First dose of buprenorphine should generally be 4 mg, with review of the patient 2 - 4 hours later (or early the following day)
Patient expectancy	Patients who are not prepared for the possibility of precipitated withdrawal are more likely to be distressed and confused by its onset, with potential negative consequences (e.g. treatment drop-out, abuse of other medications).	Inform patients fully (and carers where relevant). Provide written information. Prepare a contingency management plan for severe symptoms.
Use of other medications	Symptomatic medication (eg clonidine) can be useful in relieving any precipitated withdrawal.	Prescribe and dispense in accordance with a management plan

### Transferring to buprenorphine from doses of methadone of 40 mg or less:

Wherever possible, patients should be on a methadone dose of less than 40 mg (and preferably 30 mg or less) for at least one week prior to receiving their first dose of buprenorphine. Indeed, it is preferable for patients to be experiencing a mild degree of methadone withdrawal prior to converting to buprenorphine. For many patients, the optimal methadone dose prior to transferring to buprenorphine may be below 30 mg of methadone.

The following conversion rates should be used when converting from low-dose methadone to buprenorphine.

Last Oral Methadone Dose (mg)	Initial Buprenorphine Dose (mg) (S/L tablet)	Day 2 Buprenorphine Dose (mg) (S/L tablet)
20 - 40 mg	4 mg	6 to 8 mg
10 - 20 mg	4 mg	4 to 8 mg
1 - 10 mg	2 mg	2 to 4 mg

**The first dose of buprenorphine should be administered at least 24 hours after the last methadone dose, and at least 6 hours after last heroin use.**

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. A precipitated withdrawal may be avoided 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.

e.g. Last dose of methadone – early morning; 1st dose buprenorphine – late next day

Features of a precipitated withdrawal following the first dose of buprenorphine are typically mild to moderate in severity, which can distress the unprepared patient. Symptoms commence 1 - 4 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 (eg clonidine 100 mcg 3 - 4 hourly). Subsequent doses of buprenorphine (the following day) are less likely to precipitate withdrawal symptoms.

**Transferring to buprenorphine from doses of methadone greater than 40 mg (ie where there is a risk of relapse to heroin on lower dose)**

Most patients in methadone treatment require maintenance doses of greater than 40 mg of methadone to achieve abstinence from heroin, and are unable to reduce their dose of methadone to 40 mg or less without considerable withdrawal discomfort or relapse to heroin use. As it may be difficult to get these patients' doses of methadone below 40 mg, transfer to buprenorphine may need to be considered at higher methadone doses, with the inherent risks associated with such a procedure explained fully to the patient.

It is possible to transfer to buprenorphine from methadone doses of 40 - 60 mg for those patients who choose to do so. *The general principle is to cease methadone dosing, and delay the initiation of buprenorphine treatment until the patient experiences significant, observable features of opioid withdrawal. This generally means that buprenorphine is not commenced until 48 - 96 hours after the last dose of methadone.* Patients should be warned that the use of heroin or other opioids at this stage increases the likelihood of a difficult initiation to buprenorphine. Symptomatic withdrawal medication may be prescribed to ease the

discomfort of methadone withdrawal, although the quantities of medications, such as benzodiazepines or clonidine, should be limited. Medications containing codeine or d-propoxyphene should be avoided.

### **Prepare the patient for withdrawal symptoms**

Patients should have the possibility of precipitated withdrawal explained, as well as the relevant strategies for dealing with its symptoms. Transfer should be organised for a time when the patient has no significant work or other commitments, and the doctor is available for review.

**Patients should be reviewed by their prescriber immediately prior to commencing buprenorphine, to ensure they are indeed in opioid withdrawal.**

### **The first dose of buprenorphine should be 4 mg.**

**After first dose, later the same day** (approximately 3 - 4 hours after the first dose of buprenorphine): Review by medical practitioner.

- If patient is experiencing no increase in withdrawal severity, either subjectively or objectively, give another 2 or 4 mg of buprenorphine.
- If patient is experiencing a worsening of withdrawal, give no further dose that day. Symptomatic withdrawal medication may be required for the rest of the day (eg clonidine 100 mcg 3 - 4 hourly).

NB. Peak withdrawal discomfort is experienced during the first day of buprenorphine treatment.

**Second day:** Review by the prescriber prior to dosing on the following day.

Dose can generally be increased to 6 or 8 mg.

**Subsequent days:** Subject to review of the patient by the prescriber, further increases.

Patients may not feel entirely comfortable during the whole first week. The recommended procedure for transferring patients from medium doses of methadone (e.g. 40 - 60 mg) to buprenorphine is summarised in the following table.

TABLE 4  
SUMMARY OF  
PROPOSED PROCEDURES FOR MEDIUM DOSE METHADONE (40 - 60 MG) TO  
BUPRENORPHINE TRANSFER

---

1. Prepare the patient for the transition. Provide information, organise supports, communicate with pharmacist and/or other staff.
  2. Cease methadone dose and delay first buprenorphine dose until the patient experiences significant withdrawal discomfort (generally 48 - 96 hours after last methadone dose). Symptomatic medication (limited amounts) may be required.
  3. Administer first dose of 4 mg buprenorphine in the morning or early afternoon.
  4. Review the patient 2 - 4 hours after first buprenorphine dose:
    - Worsening of withdrawal following first dose → provision of symptomatic medication for opioid withdrawal for remainder of the day;
    - no worsening, or an improvement, in withdrawal following the first dose → a further 2 to 4 mg of buprenorphine dispensed that afternoon / evening
  5. Review the patient prior to dosing on the following day. Titrate the dose of buprenorphine to 6 - 10 mg, according to response on previous day.
  6. Review frequently and titrate dose until stable. Patients may continue to describe mild withdrawal features and/or dysphoria for one to two weeks after transfer.
- 

**It is strongly recommended that patients on methadone doses of greater than 60 mg reduce their dose to 60 mg or less prior to attempting transfer. Patients unable to reduce to these levels of methadone should not attempt transfer to buprenorphine.**

### 3.3 Stabilisation

The optimal maintenance dose needs to be individualised according to the patient's response to buprenorphine. People's responses vary considerably, according to the following factors:

1. rates of absorption or metabolism of buprenorphine;
2. levels of opioid neuroadaptation and dependence;
3. experience of side-effects;
4. continued use of other drugs.

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

**Early doses can be test doses.** Initial doses of buprenorphine can serve as ‘test doses’ to enable both patient and clinician to monitor responses to the medication. In some people they may not be adequate to prevent withdrawal over a 24-hour period, while they may make some people feel sedated or ‘drugged’ (due to additional drug use, or to the initial dose of buprenorphine being too high).

**Prompt results.** Equilibrium levels with buprenorphine are achieved quickly, and the effects of a dose-change should become apparent within 2 - 3 days. Consequently, dose levels of buprenorphine can be more rapidly titrated according to patient response, than can methadone.

**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)*

**Regular patient review**

Frequent reviews by the prescriber are required in the first few weeks:

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

As treatment progresses, the prescribing doctor should review the patient 2-3 times a week until stabilised:

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

**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.**

**The following minimal schedule of reviews is recommended by treating doctors or their nominees <sup>2</sup>:**

- *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 2 - 4 days until stabilisation.*
- *Every week during the following 4 – 6 weeks.*
- *Every two weeks during the following 6 – 8 weeks.*
- *Monthly reviews thereafter, although the prescriber may wish to extend reviews to up to 3 months for very stable patients.*

---

<sup>2</sup> In practice, a suitably trained nurse or pharmacist often undertakes these reviews, with reference to the prescribing doctor where necessary.

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

**Dose increases should be made only after review of the patient by the prescribing doctor.**

If daily reviews can be organised by the prescriber, daily increases can be accommodated. Practically, however, most prescribers may not be able to review the patient more than every two or three days (eg because of sessional practice or weekends). A period of 2 - 3 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).

**Changes in buprenorphine dose**

The dose response curve of buprenorphine indicates that small increments have a greater impact at low doses, whereas at higher doses, larger changes are required for a substantial change of effect. The following increments are proposed:

- Below 16 mg buprenorphine : dose changes of 2 - 4 mg
- Above 16 mg buprenorphine : dose changes of 4 - 8 mg

**Titrating the dose of buprenorphine**

At each review, the buprenorphine dose should be titrated according to the following parameters:

- features of intoxication or withdrawal over preceding 24 hours (self-report, examination);
- cravings for heroin use;
- additional drug use (heroin and other drugs), and reason stated by patient for using;
- side-effects or other adverse events (including intoxicated presentations, overdoses);
- adherence with dosing regime (attendance for dosing, route of administration);
- patient satisfaction with buprenorphine dose and treatment.

The following should guide prescribers in determining the buprenorphine dose.

Decrease buprenorphine dose	Maintain buprenorphine dose	Increase buprenorphine dose
Features of intoxication to buprenorphine (eg sedation) particularly at peak effect times (1 – 4 hours after dosing)	No features of withdrawal or intoxication	Features of withdrawal over preceding 24 hours, increasing in the period immediately prior to the next dose
		No features of intoxication to buprenorphine, particularly at peak effect times (1 - 4 hrs after dosing)
	Low cravings for heroin or other drugs	Intense cravings for heroin in past 24 hrs or heroin use to avert withdrawal

## Regular and high risk use of heroin

Stabilisation with prescribed opioids is hard to achieve if the patient is in the habit of using additional opioids (eg heroin, codeine preparations), as they complicate the interpretation of withdrawal or intoxication effects. In particular, patients who continue to use heroin during the first few doses of buprenorphine may experience difficulties in stabilising on the new medication. The patient should be encouraged to make every effort to avoid heroin, or any other opioid, in the period prior to dosing.

## 3.4 Maintenance dosing

### Dose levels

Buprenorphine doses need to be individually titrated according to the patient's response to treatment. Effective maintenance doses, resulting in reduced heroin use and improved treatment retention, are achieved with high buprenorphine doses in the range of 12 - 24 mg per day. Some patients may be satisfactorily maintained on daily doses of 8 - 12 mg, while doses of 4 mg or less will not be as effective in retaining patients in treatment or reducing heroin use (similar to, or worse than, the outcomes associated with methadone doses of 20 mg). There is little evidence to suggest that daily doses higher than 24 mg will result in improved outcomes or effects, and little is known regarding the nature of adverse events at maintenance daily doses greater than 32 mg. **The maximum daily dose of buprenorphine routinely recommended is 32 mg.**

**Effective maintenance doses, which reduce heroin use and improve treatment retention, are achieved with buprenorphine doses in the range of 12 - 24 mg per day. The maximum recommended daily buprenorphine dose is 32 mg.**

People wishing to reduce their use of heroin, or other opioids, can do so with increases in the substitution dose of buprenorphine, as higher doses of this substance produce more effective antagonist reactions, blocking the effects of additional heroin use.

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

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

Buprenorphine dosing begins on a daily basis. Most clinical studies with this therapy have examined daily dosing regimes, but recent studies indicate that many patients who are stabilised on buprenorphine can be maintained on alternate-day dosing, some even on three-times-a-week dosing, without experiencing features of intoxication or withdrawal.

The convenience of reduced-frequency dosing should be considered for all patients found suitable for a trial of alternate-day dosing, i.e. if they meet the following conditions:

- on a stable dose of buprenorphine for at least two weeks;
- having no high-risk drug use (high-risk drug use refers to 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).

However, not all patients will be suited to an alternate-day, or three-times-a-week, dispensing regime, as some will experience increased cravings or features of withdrawal on the non-dosing days.

**Estimates suggest that about 15% of patients are more comfortable and more effectively maintained on daily, rather than alternate-day, dosing regimes.** It is recommended that suitable patients initially be trialed for two weeks on an alternate-day dosing regime of buprenorphine. If this is successful, the patient can then be trialed 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.

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 32 mg dosed at a time).* The patient should be reviewed following the first or second 48-hour dose, and the dose titrated according to the response:

- If the patient reports features of intoxication from the buprenorphine during its peak effects (within the first 24 hours), the 48-hour dose should be reduced.
- If the patient reports that the dose *does not* prevent the onset of opioid withdrawal or cravings over a 48-hour period, then the 48-hour buprenorphine dose should be increased.

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 after 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 = 3 times the normal 24 hr dose if 24 hr buprenorphine dose < 12 mg*

*3-day dose = 32 mg when 24 hr buprenorphine dose ≥ 12 mg*

The patient should be reviewed in the week following the first 72-hour dose, and the dose titrated accordingly. If a patient cannot be stabilised on a three-times-a-week dosing regime, the four-times-a-week dosing regime should be considered.

TABLE 5

Buprenorphine S/L dose (mg)		
Daily dose (24 hrs)	Two day dose (48 hrs)	Three day dose (72 hrs)
2	4	6
4	8	12
6	12	18
8	16	24
10	20	30
12	24	32
14	28	32
16	32	32
18	32	32
20	32	32
22	32	32
24	32	32
26	32	32
28	32	32
30	32	32
32	32	32

Some patients attempting alternate-day dosing may benefit from doses greater than 32 mg, however, there is limited evidence regarding the safety of higher doses, and buprenorphine is registered in Australia with a maximum recommended dose of 32 mg. Practitioners should be aware of the medico-legal implications of off-label prescribing before they prescribe doses of greater than 32 mg. **Frequent clinical and hepatic monitoring is recommended under such circumstances.**

### 3.5 Take-away doses

“Take-away” is medication not administered by the dispensing clinician, but given to the patient for administration at a later time. In Victoria, buprenorphine is provided in a supervised dosing program. As with methadone, no take-away doses are permitted in the first two months of treatment. After that time, prescriber-authorized take-away dose(s) for special circumstances up to once a month, to allow up to 72 hours without supervised dosing, are permitted without approval from the Drugs and Poisons Section. Stable methadone patients transferring from methadone will be eligible for take-away dose(s) under the same special circumstances once they are stable on buprenorphine without the need to wait an additional two months.

#### The benefits of take-away opioid doses:

1. they emphasise and promote patients’ responsibility for their own treatment ;
2. they enhance the patients’ integration into the community by cutting time and travel costs associated with the treatment;
3. they tend to promote patient retention by minimising the inconvenience of regular attendance for doses. (Studies show take-away policies produce better retention rates than programs which restrict take-away doses).
4. They benefit pharmacists by reducing the inconvenience and cost of daily dispensing.

### Concerns regarding take-away doses of opioid medications:

1. **Possible overdose or accidental dose:** Take-aways increase the risk of deliberate or accidental overdose by the patient or others, particularly children and other non-tolerant individuals, and by any one of these in combination with other sedative drugs.
2. **Injection of take-aways,** resulting in overdose, damage to veins or other health consequences.
3. **Doubtful or poor compliance:** Diversion to others of take-aways, resulting in poor outcomes for patient (poor compliance with treatment regime), and abuse by other individuals.
4. **Diversion** of buprenorphine to heroin-dependent individuals or methadone maintenance patients and precipitation of withdrawal
5. **Bad ‘publicity’** over treatment regime - “just another drug being bought and sold”.

<p style="text-align: center;"><b>Uncontrolled access to take-aways → more diversion and increased adverse consequences.</b></p>
--

### The main issues regarding the safety of take-aways are:

- a) **Discerning suitability.** Close monitoring by the provider is vital to decide which patients are suitable for take-aways, and this monitoring is not always achievable in community programs.
- b) **Education of the patient** regarding safe and responsible handling of the take-away doses.

### Absence from pharmacy in patients ineligible for take-away doses

**The “one-off” supervised multiple dose.** In circumstances where a patient is ineligible for buprenorphine take-aways (eg recently commenced treatment, high-risk drug use), but is unable to attend for dosing for one or two days, it is possible to organise a one-off supervised multiple-dose of buprenorphine (as administered to patients engaged in alternate-day or three-times-a-week dispensing). In this way, the dose of buprenorphine can be doubled in circumstances where the patient is away from the pharmacy for one day, or increased by 3 times the daily dose (to maximum of 32 mg) where the patient cannot attend the pharmacy for 2 consecutive days.

## 3.6 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 positively encouraged to avail themselves of counselling services. However there is no real place for mandatory attendance at counselling sessions, and all ancillary services should be offered on the basis of the patient freely consenting to be involved.

Counselling approaches, such as motivational interviewing, relapse prevention and social skills training, which are based on cognitive behavioural therapies, are frequently used and found to be effective. More intensive psychotherapy can be beneficial to people with concomitant affective disorders (e.g. anxiety, depression).

### **3.7 Continued high-risk drug use**

**People are said to be in continued high-risk drug use when there are frequent intoxicated presentations or overdoses of heroin or other substances, 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; *and*
  - × daily dosing regimes.

*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:
  - (a) there is little or no response to an increase in medication;
  - (b) the patient is already on a high dose of medication; *or*
  - (c) an increase in dose is considered ‘unsafe’ by the prescriber.
- Alternatively, non-pharmacotherapeutic treatment options should be considered (e.g. therapeutic communities, counselling and support), and the patient withdrawn from prescribed opioid medication.

## 3.8 Missed Doses

### Single dose missed

Sometimes a patient who is on an alternate-day or three-times-a-week regime misses a 'dosing day', attending 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 - 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 the 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 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.

### Multiple doses missed

Patients who have erratic attendance for dosing are unlikely to achieve optimal outcomes. Patients who have missed more than five consecutive days of buprenorphine must be reviewed by their prescribing doctor prior to receiving a further dose, to ensure their safety.

**The recommended recommencement doses of buprenorphine are:**

Usual 24 hour buprenorphine dose	Recommencement dose
> 8mg	8mg if < 7 days with no dose 4 mg if 7 days or more with no dose
6 - 8 mg	4 mg
2 - 4 mg	2 – 4 mg

Patients can be brought up to their usual maintenance doses over subsequent days (using dosing increments discussed earlier) if clinician and patient think this is appropriate.

### 3.9 Cessation of buprenorphine maintenance treatment

#### Withdrawal from buprenorphine maintenance treatment

##### *Nature of withdrawal from buprenorphine maintenance treatment*

There is some clinical and anecdotal evidence that withdrawal from buprenorphine is less prolonged and less severe than methadone withdrawal, but the research on this is not conclusive. Withdrawal does appear to be milder during buprenorphine dose reductions, and the rate of buprenorphine dose-reduction is normally more rapid than with methadone. The symptoms and signs of withdrawal from buprenorphine are qualitatively similar to withdrawal from other opioids.

##### **Common pattern of long-term withdrawal of buprenorphine treatment:**

- The onset of symptoms is usually around 24 - 72 hours after the last 24-hour dose.
- Symptoms peak around days 3 - 5 following short maintenance courses of buprenorphine treatment (weeks / months), or days 5 - 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) are likely to 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**

Evidence from methadone research suggests that long-term outcomes of treatment are enhanced by:

- **Longer treatment episodes.** Evidence from methadone research suggests that long-term outcomes are enhanced by longer treatment episodes (for example, more than 12 months).
- **A more stable and supportive lifestyle.** The longer treatment episode allows the opportunity for the patient to establish a lifestyle away from heroin and other drug use prior to withdrawing from methadone treatment. Premature withdrawal from methadone

(before the patient has achieved a degree of stability in social circumstances and drug use) is more likely to be associated with a relapse into dependent heroin use.

The likelihood of premature withdrawal from maintenance treatment is reduced by:

- **A well-informed patient, with all the facts about the maintenance program.** 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. Patient literature is now available regarding withdrawal from methadone treatment (Dunlop *et al* 1996), and parallels can be made with withdrawal from buprenorphine. Despite withdrawal from buprenorphine being frequently described as milder than from other opioids, patients should be informed of the likely withdrawal profile.

Except in the case of involuntary withdrawal (see below), withdrawal from buprenorphine should occur only with the consent of the patient. Graduated reduction over weeks results in better outcomes (less relapse to heroin use) than rapid reductions. The following rates of dose-reduction are proposed, although reductions can occur both more rapidly and more slowly:

TABLE 6  
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

An increase in heroin or other drug use, or a worsening of the patient’s physical, psychological or social well-being, may warrant a temporary cessation or slowing-down of the reduction rate.

### Supportive Care

Patients should be aware of their dose, except where an agreement has been reached between patient and service provider to the administration of a ‘blind dose’. 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, anti-diarrhoeal agents, hypnotics, and smooth muscle relaxants (eg hyoscine) for patients experiencing severe withdrawal. However, caution should be applied regarding the use of potential drugs of abuse (eg benzodiazepines).

### Involuntary withdrawal (without patient consent or against patient’s wishes)

The conditions for involuntary termination 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.

The rate of reductions under circumstances of involuntary treatment cessation can be faster (e.g. up to 4 - 8 mg reductions every 3 - 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.

## **The use of buprenorphine to assist withdrawal from methadone maintenance programs**

Many patients on long-term methadone maintenance programs experience considerable difficulties in conventional approaches to withdrawing from methadone, including a prolonged period of withdrawal discomfort and/or relapse to heroin use. Consequently, there is considerable interest in finding alternative methods of withdrawing from methadone maintenance programs.

Two approaches have been recently proposed:

1. the use of opioid antagonists (rapid opioid withdrawal techniques), *and*
2. transfer to buprenorphine.

The latter approach entails a reduction in the dose of methadone, transfer to buprenorphine, and subsequent withdrawal from buprenorphine. *As there is limited experience or evidence to support these approaches, they cannot be generally recommended at this time.*

## **Commencing naltrexone following buprenorphine maintenance treatment**

There is limited experience in commencing naltrexone following the cessation of maintenance buprenorphine treatment. The initiation of naltrexone must be delayed until several days after the last dose of a full opioid agonist (generally 7 days after heroin use and 10 - 14 days after methadone use). However, naltrexone can generally be initiated within days of the last dose of buprenorphine. The following procedures are recommended.

- In circumstances where the last dose of buprenorphine was 2mg (or less) for at least one week, naltrexone can be initiated 4 - 5 days after the last dose of buprenorphine (providing there has been no heroin use in the previous 7 days).
- Where the last dose of buprenorphine was greater than 2 mg, and to reduce the likelihood of precipitating withdrawal symptoms, the first dose of naltrexone can be delayed until more than 7 days after the last buprenorphine dose.

- 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 (up to 150 mg 3 - 4 hourly), benzodiazepines (eg diazepam up to 5 - 10 mg every 3 - 4 hours as needed), metoclopramide, hyoscine butylbromide and NSAIDS.
- Subsequent doses of naltrexone can be 25 mg for a further 2 - 3 days and then 50 mg per day as usually recommended. Clinical guidelines regarding the use of naltrexone should be consulted (Bell *et al* 1999).

**The high receptor affinity of buprenorphine complicates the interpretation of a naloxone challenge test prior to commencing naltrexone in patients transferring from buprenorphine:**

- a negative naloxone challenge test does not preclude the onset of withdrawal on commencing naltrexone;
- a positive naloxone challenge test is likely to reflect recent use of other opioids, and indicates that naltrexone induction should be delayed.

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.**

**Transferring to methadone**

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

- 1. Intolerable side effects to buprenorphine.**
- 2. 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
- 3. Where 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.
- 4. 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 additional 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 from methadone to buprenorphine.

**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. 4 mg or less) should be commenced on lower doses of methadone (e.g. 20 mg methadone or less). The methadone dose can then be titrated accordingly. Care should be taken not to increase the dose of methadone too quickly, as buprenorphine can 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.

## SECTION 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 (DSM IV, 1994). The characteristic features of heroin withdrawal are shown in the following table.

TABLE 7  
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, leg cramps, twitching, arthralgia
Piloerection, pupillary dilatation, elevated blood pressure, tachycardia.
Anxiety, irritability, dysphoria, disturbed sleep, increased cravings for opioids

---

Physical symptoms generally commence 6 - 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. It can, however, significantly complicate concomitant medical or psychiatric conditions.

#### Objectives of withdrawal services

Heroin users present for 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 resulting in prolonged periods of abstinence. Indeed, research suggests that withdrawal treatment alone has little, if any, long-term impact on levels of drug use<sup>1-4</sup>. Unfortunately, many patients, families, friends, and health and welfare professionals hold unrealistic expectations regarding the outcomes of withdrawal services. Many are

---

<sup>1-4</sup> Mattick, R.P., & Hall, W. (1996). Are detoxification programmes effective?. *Lancet* 1996; 347: 97-100.

Hubbard, R.L., Marsden, M.E., Rachal, J.V., Harwood, H.J., Cavanaugh, E.R., & Ginzburg, H.M. (1989). Drug abuse treatment a national study of effectiveness. University of North Carolina Press: North Carolina.

Vaillant, G.E. (1988). What does long term follow up teach us about relapse and prevention of relapse in addiction. *British Journal of Addiction*, 83, 1143-57.

Simpson, D.D. & Sells, S.B. (1982). Effectiveness of treatment for drug abuse: An overview of the DARP research program. *Advances in Alcohol and Substance Abuse*, 2, 7-29.

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.

### **It helps to set sensible withdrawal objectives**

#### **A realistic set of objectives for withdrawal services would be:**

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, or dehydration in an individual with poor baseline nutritional status.
  - 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 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 it for a set period of time afterwards. However, giving up entirely is not the goal of every patient. Many see withdrawal as a means of **reducing** levels of heroin use, the severity of their dependence and some of its associated harms. So, although the cessation of heroin use is an optimal outcome, a reduction in heroin use during a withdrawal attempt may still represent a very positive outcome for patients.
4. *To get patients help with any other problems.* 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. But 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 managing heroin withdrawal

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

- assessment,
- treatment-matching,
- planning for withdrawal, *and*
- supportive care.

The assessment of patients presenting for treatment was discussed in Section 2.3.

### Treatment selection

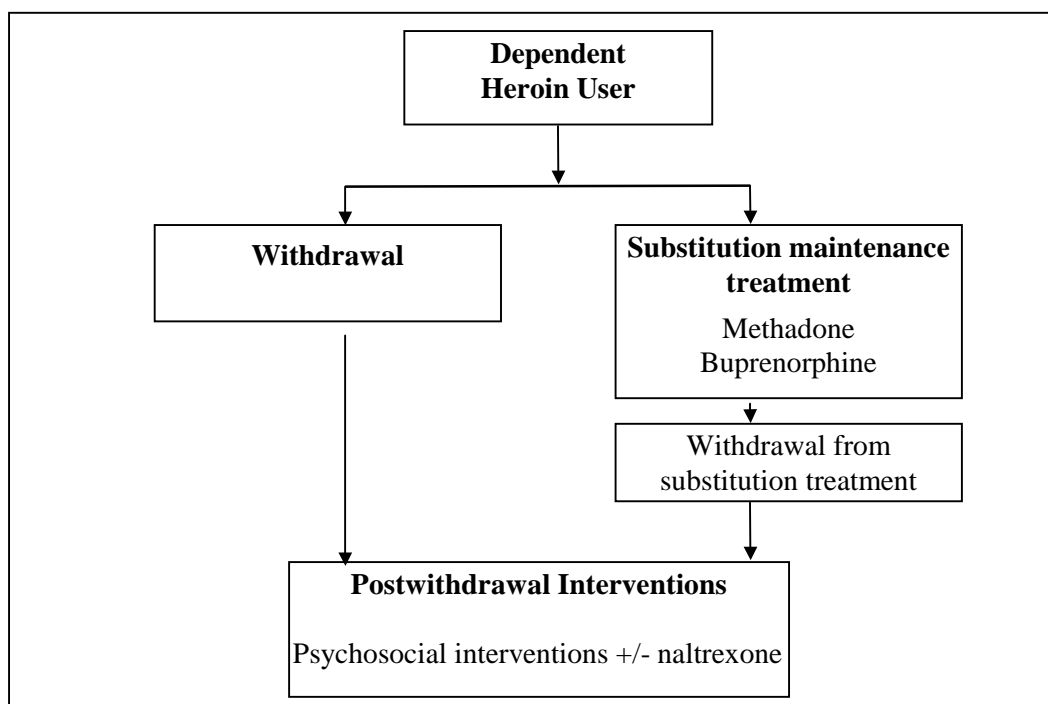
#### *Range of Treatments*

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 1.

FIGURE 1  
TREATMENT PATHWAYS FOR DEPENDENT HEROIN USERS



In general, withdrawal treatment (such as naltrexone, residential rehabilitation programs, counselling or 12-step programs), is appropriate for those who are considering abstinence-oriented, post-withdrawal treatment, 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. 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 2).

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 the way to go, if it's what the patient really wants. 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 a switch will be made to an alternative treatment pathway.

TABLE 8  
**COMPLEX PRESENTATIONS REQUIRING RESIDENTIAL  
 WITHDRAWAL SERVICES**

Criteria for intensive residential settings (e.g. inpatient withdrawal unit)
<ul style="list-style-type: none"> <li>• Unstable medical / psychiatric condition;</li> <li>• Polydrug dependence and withdrawal from multiple drugs;</li> <li>• Unclear medical, psychiatric or drug-use histories requiring close monitoring in a supervised environment.</li> </ul>
Criteria for supported residential setting (e.g. community withdrawal unit)
<ul style="list-style-type: none"> <li>• Unsupportive home environment, such as with other drug users, or without anyone reliable to supervise and support the patient;</li> <li>• Repeated failure at outpatient withdrawal.</li> </ul>

*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. Unfortunately, such inpatient services often have waiting-lists of days or weeks, and the patient 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**

**Provision of information and strategies for coping.**

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 for support 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 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 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 3).

## **Monitoring**

An important part of withdrawal service 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 (eg alcohol and drug worker, general practitioner, or experienced pharmacist) at least daily during the first few days of treatment.

## **Objective and Subjective Withdrawal Scales**

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 the *Subjective Opioid Withdrawal Scale and Objective Opioid Withdrawal Scale* are provided in Appendix 2.

## 4.3 Overview of buprenorphine in the management of heroin withdrawal

### Efficacy of buprenorphine compared to other withdrawal medication regimes (literature review)

The efficacy of buprenorphine in the management of heroin withdrawal has been compared to other withdrawal approaches in several randomised controlled trials conducted in inpatient<sup>(1-3)</sup> and outpatient settings<sup>(4-6)</sup>.

In general, these studies have demonstrated buprenorphine to be:

- more effective than symptomatic medications in reducing withdrawal symptoms<sup>(1, 2, 3, 5, 6)</sup>,
- more effective in retaining patients through the withdrawal episode and in post-withdrawal treatment<sup>(6)</sup>; and
- more effective in reducing heroin use in outpatient settings<sup>(6)</sup>.

Readers are referred to the *Cochrane Review on Buprenorphine for Opiate Withdrawal*.

**In the medically ill.** Controlled trials comparing buprenorphine with other withdrawal medications for the management of heroin withdrawal in medically-ill patients have not been conducted. Nevertheless, uncontrolled studies have reported favourably on the use of buprenorphine in these circumstances. 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 or the intoxication of the patient.** 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:

---

<sup>1</sup> Cheskin LJ, Fudala PJ, & Johnson RE (1994). A controlled comparison of buprenorphine and clonidine for acute detoxification from opioids. *Drug and Alcohol Dependence*, 36(2), 115-21;

<sup>2</sup> Nigam AK, Ray R, & Tripathi M. (1993). Buprenorphine in opiate withdrawal: A comparison with clonidine. *Journal of Substance Abuse Treatment*, 10, 391-394;

<sup>3</sup> O'Connor PG, Carroll KM, Shi J, Schottenfeld RS, et al (1997). Three methods of opioid detoxification in a primary care setting. *Annals of Internal Medicine* 127(7) 526-530;

<sup>4</sup> Bickel WK, Stitzer ML, Bigelow GE, Liebson IA, et al (1988). A clinical trial of buprenorphine: Comparison with methadone in the detoxification of heroin addicts. *Clinical Pharmacology & Therapeutics*, 247, 47-53;

<sup>5</sup> Schneider U ;

<sup>6</sup> Lintzeris N, Bell J, Bammer G, Rushworth L et al (2000) A randomised controlled trial of buprenorphine for the management of outpatient heroin withdrawal. paper presented at the November 2000 National Methadone Conference, Melbourne, Australia.

- 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 dosing in withdrawal**

Over-dosing doesn't help  
Under-dosing doesn't help

Problems encountered may not be the fault of the medication dose

### **Preventing precipitated withdrawal on commencing buprenorphine**

**Buprenorphine can precipitate opioid withdrawal in someone who has recently used heroin (within the past 6 hours) or methadone (See Section 3.2).** Buprenorphine-precipitated withdrawal typically commences 1- 4 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 (eg clonidine 100 mcg 3 - 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.** In practice, it is recommended that patients wait at least 6 hours after their last use of heroin prior to receiving their first buprenorphine dose. It is preferable to withhold the first dose until the patient is beginning to experience the early features of withdrawal. 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 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 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 to this rule is when patients experience difficulty sleeping during withdrawal, and may benefit from the limited use of benzodiazepines as a hypnotic. However, benzodiazepines should not be used

routinely from the outset of the withdrawal episode, but rather should be added, as required, following clinical review of the patient. Low doses of a hypnotic (eg temazepam 10-20 mg nocté, oxazepam 15-30 mg nocté or nitrazepam 5-10 mg nocté) are recommended, with daily dispensing from the pharmacy (or supervised by a responsible adult). Under normal circumstances, benzodiazepines should not be continued beyond several days, with non-pharmacological approaches being encouraged (sleep hygiene strategies).

### **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.

**It is very important for patients to abstain from heroin use until they are stabilised on buprenorphine.**

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, and tricyclic antidepressants, 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. Intoxicated patients should not be dosed with buprenorphine or sedative medications.

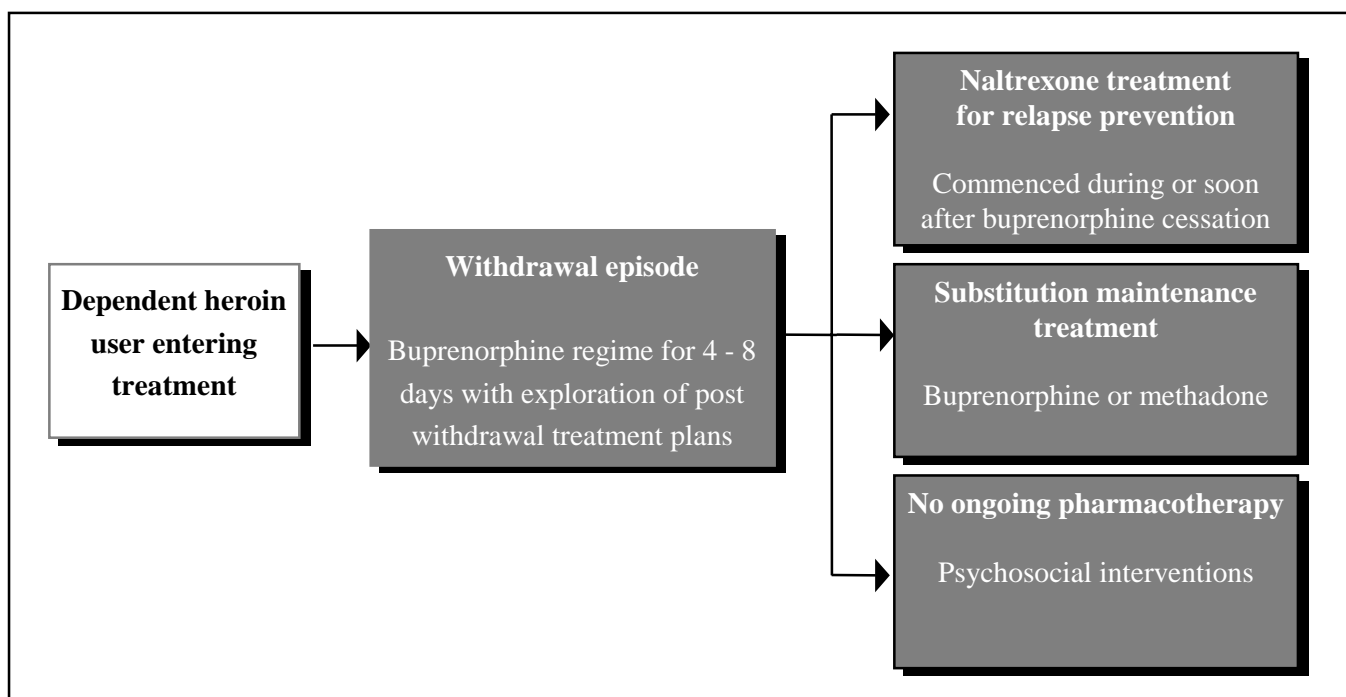
### **Gateway model of treatment with buprenorphine**

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. Many patients entering withdrawal treatment do so without necessarily having considered all their treatment options, simply ‘hoping’ that an attempt at withdrawal will be sufficient to stop heroin use.

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. (On many other withdrawal medications, such as benzodiazepines or clonidine, patients are either so psychologically distressed or so heavily sedated 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. For those patients who have successfully refrained from heroin use during withdrawal, and who are considering longer-term naltrexone treatment, naltrexone can be initiated either during buprenorphine administration or after a short course is ceased. Patients who are not interested in ongoing pharmacotherapy treatment can cease 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. Care should be exercised in transferring patients with short histories of heroin dependence from short-term withdrawal programs on to long-term substitution maintenance programs. These treatment pathways are shown in Figure 2.

FIGURE 2.  
GATEWAY MODEL OF TREATMENT WITH BUPRENORPHINE



#### 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.

**The recommended duration of treatment with buprenorphine for the management of heroin withdrawal is 4 - 8 days.** This short regime ensures the treatment covers the time when heroin withdrawal symptoms are most severe (typically up to 4 or 5 days), and then is promptly discontinued, thereby minimising rebound withdrawal phenomena and limiting the duration of withdrawal discomfort.

There is no conclusive evidence of an optimal buprenorphine dosing regime for heroin withdrawal. In general, daily buprenorphine doses of 4 - 16 mg appear to be most effective in reducing withdrawal severity and heroin use. The reader is referred to the Cochrane Review, for an analysis of relevant studies. The following short-term outpatient withdrawal regime is recommended:

**TABLE 9**  
**RECOMMENDED SHORT OUTPATIENT REGIMES**

	Proposed regime	Recommended lower and upper limits
Day 1	6 mg	4 to 8 mg
Day 2	8 mg	4 to 12 mg
Day 3	10 mg	4 to 16 mg
Day 4	8 mg	2 to 12 mg
Day 5	4 mg	0 to 8 mg
Day 6		0 to 4 mg
Day 7		0 to 2 mg
Day 8		0 to 1 mg
Total dose	36 mg	

Some flexibility is allowable in doses to accommodate a range of factors, such as amount of heroin use and psychological condition, impacting 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.

**Titration: 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.**

Flexible dosages 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).

It is a good idea to attempt a short-term regime, and schedule a formal review of progress within a few days. At this review, the clinician and patient can together consider the available post-withdrawal treatment options (see Section 4.6).

Those patients who remain ambivalent about long-term post-withdrawal treatment, and 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.

**However, there are good reasons for not prolonging buprenorphine treatment:**

- Intake for more than several days commonly produces rebound withdrawal when ceased, typically starting 1 - 3 days after the last dose of buprenorphine, peaking 2 - 5 days after the last dose, and with some symptoms persisting 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.

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 distressing 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 2 - 3 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 5 PM and 10 PM) is recommended**, to allow relief of withdrawal symptoms until the morning. *N.B Buprenorphine should not be administered if there are any features of intoxication or sedation.*

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

**TABLE 10  
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

### Transition to maintenance treatment

#### *Buprenorphine maintenance treatment.*

Transition to a buprenorphine maintenance treatment program simply requires the continuation of treatment, often with upward titration of the dose to achieve optimal maintenance dose levels (eg. 12 - 24 mg per day). The reader is referred to Section 3.

#### *Methadone maintenance treatment*

The transition to methadone maintenance treatment requires the cessation of buprenorphine, with the first dose of methadone given at least 24 hours later. The reader is referred to Section 3.9 of these guidelines.

### Commencing naltrexone treatment after short duration buprenorphine withdrawal

**Seven-day abstinence:** One of the difficulties for many heroin users in commencing naltrexone treatment is staying off heroin for a whole week before the first dose, to avoid the precipitation of withdrawal. The recommended 7-day opioid-free period (Bell *et al* 1999) also limits the use of opioids (such as methadone, codeine or d-propoxyphene) as withdrawal medications, as they delay even further the initiation of naltrexone treatment.

The pharmacology of buprenorphine allows the commencement of naltrexone without major delays. This is thought to be because buprenorphine has a higher affinity for opioid receptors than naltrexone, so the naltrexone does not significantly displace buprenorphine or cause the precipitation of severe opioid withdrawal.

**From buprenorphine to naltrexone:** Researchers are yet to determine the optimal method of inducing on to naltrexone from buprenorphine treatment, but two general procedures have been used:

1. commencing low doses of naltrexone whilst continuing buprenorphine;
2. ceasing buprenorphine and commencing naltrexone several days later.

Sample dosing regimes for the two approaches are shown in the following table.

**TABLE 11**  
**NALTREXONE INDUCTION REGIMES**

Day	Sample buprenorphine regime (S/L tablets)	Early NTX induction regime (oral)	Delayed NTX induction regime (oral)
1	6 mg	0	0
2	10 mg	0	0
3	8 mg	12.5 mg	0
4	6 mg	12.5 mg	0
5	4 mg	25 mg	0
6		50 mg	0
7		50 mg	0
8		50 mg	0 or 12.5 mg
9		50 mg	12.5 mg
10		50 mg	25 mg
11		50 mg	50 mg

The potential advantages and disadvantages of each approach are explored in Table 12 below.

**Which procedure is best?**

*Both procedures result in an increased severity of opioid withdrawal following the first dose of naltrexone. This typically commences 90 minutes to 4 hours after the first naltrexone dose, peaks around 3 – 6 hours after the naltrexone dose, and generally subsides in severity within 12 – 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 (100 – 150 mcg every 3 – 4 hours as required) and a benzodiazepine (eg diazepam 5 mg 3 – 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.*

**Outpatient setting is suitable only:**

- where there is a suitable and responsible person to support the patient where they live, and to supervise medications; *and*
- if the prescribing doctor is available to address any potential complications.

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

**TABLE 12**  
**COMPARISON BETWEEN EARLY AND DELAYED NALTREXONE INDUCTION**

	Early NTX induction regime	Delayed NTX induction regime
Potential advantages	<p>Only 36 –48 hours of abstinence from heroin use is required prior to first dose of naltrexone; hence more patients will get a first NTX dose</p> <p>More rapid resolution of withdrawal discomfort: NTX-precipitated withdrawal peaks early in withdrawal episode, following NTX dose, with resolution of most withdrawal symptoms within days.</p>	<p>Allows more time for consideration and selection of optimal post-withdrawal treatment options</p> <p>Initial withdrawal episode is less severe for the patient and less intensive for service providers</p>
Potential disadvantages	<p>Greater drop-out reported after first NTX dose than in delayed induction regime</p> <p>May ‘rush’ some patients into NTX treatment, whereas other post withdrawal treatment (eg maintenance substitution treatment) may be preferred.</p>	<p>Some patients will drop out or resume heroin use prior to day 8 or 9 of withdrawal episode, and therefore not commence NTX</p> <p>NTX-precipitated withdrawal occurs later in the withdrawal episode (on day of first NTX dose)</p>

## SECTION 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 (eg 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 (eg 1 mg daily). Other commonly reported adverse events reported by the manufacturer are shown in the following table.

TABLE 13  
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 occurring 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 (eg constipation) (see Table next page).

**TABLE 14**  
**COMMON SIDE EFFECTS WITH OPIOID MAINTENANCE DRUGS**

*Not all of these may occur with Buprenorphine*

<i>Side effect</i>	<i>Common causes</i>	<i>Things that you can do</i>
Feeling drowsy after taking dose	<ul style="list-style-type: none"> <li>• Dose too high</li> <li>• Other drug use (legal or illegal)</li> </ul>	<p>Lower the maintenance dose and review other medications the patient may be taking</p> <p>Review use of sedative and other drugs affecting cognition</p>
Withdrawal symptoms maximal before next dose	<ul style="list-style-type: none"> <li>• Dose too low</li> <li>• Changes in legal or illegal drugs that patient may be using.</li> </ul>	Raise maintenance dose or review other drugs patient is taking
Withdrawal precipitated by buprenorphine dose	<ul style="list-style-type: none"> <li>• Occurs early in treatment (or after absence from treatment) when buprenorphine dose administered soon after opioid use (eg heroin methadone, morphine)</li> </ul>	Transient effect. Aim to prevent by patient education. Delay buprenorphine dose until patient experiencing opioid withdrawal
Headache	<ul style="list-style-type: none"> <li>• Common in first week of buprenorphine treatment.</li> <li>• Other causes of headache</li> </ul>	Side effect is transient and generally mild. Consider aspirin or paracetamol. Exclude other causes
Nausea	<ul style="list-style-type: none"> <li>• Common early in treatment, particularly if buprenorphine dose too high.</li> <li>• Usually mild and transient.</li> </ul>	Side-effect usually transient (days). Avoid rapid dose increases. Consider dose-reduction if persistent
Constipation	<ul style="list-style-type: none"> <li>• All opioids do this. Will be made worse by lack of dietary fibre, fluid intake or exercise</li> </ul>	Encourage fibre intake (fruit, cereals, vegetables), fluids, and regular exercise.
Weight gain, particularly for women	<ul style="list-style-type: none"> <li>• Fluid retention caused by opioids - more likely on high doses</li> <li>• Eating more while in treatment; high salt intake</li> </ul>	<p>Lower dose</p> <p>Reduce fat and salt in diet, exercise regime</p>
Poor sleep	<ul style="list-style-type: none"> <li>• Dose too low and causing withdrawal at night; or</li> <li>• Dose too late at night, causing stimulation at time of peak effects</li> <li>• Other drugs (particularly stimulants in the evening, such as coffee, nicotine, amphetamines)</li> <li>• General anxiety or irregular sleep pattern</li> </ul>	<p>Review maintenance dose and review other medications</p> <p>Follow sleep hygiene recommendations.</p>
Amenorrhoea or oligomenorrhoea	<ul style="list-style-type: none"> <li>• All opioids can do this</li> <li>• May be related to lifestyle stressors, poor diet, and general poor health</li> </ul>	<p>Periods may return after cessation of heroin use, or following withdrawal from opioids.</p> <p>Address other causes</p>
Lowered sex drive	<ul style="list-style-type: none"> <li>• More common with a high dose</li> <li>• Can be many other psychological factors (such as anxiety, poor relationship with partner etc...)</li> </ul>	Review dose
Dental problems	<ul style="list-style-type: none"> <li>• All opioids reduce saliva flow</li> <li>• Poor diet, dental hygiene</li> </ul>	Encourage teeth 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 on buprenorphine in an opioid-tolerant individual is less than that associated with the use of other opioid medications, such as methadone. 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 - 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 accidental overdose 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. *Several such deaths have been reported.*

**High doses of antagonist needed for overdose reversal:** Buprenorphine has a high affinity for  $\mu$  opioid receptors, and is not easily displaced by the antagonist, naloxone. *Doses of 10 - 30 times the normal naloxone doses used to reverse heroin overdose (up to 10 - 35 mg/70 kg) may be required to reverse the effects of buprenorphine toxicity.*

### **In the event of depression of respiratory or cardiac function:**

1. re-establish patient airway
2. begin assisted or controlled ventilation.

**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 medical officer must be notified prior to the next dose being administered.

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

## 5.4 Incorrect dose administered

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

- 1) the dispensing pharmacist (or nursing staff) should immediately notify the patient and medical officer of the error;
- 2) the patient should be warned of the likely consequences (increased sedation / 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) the patient should be monitored for at least 6 hours after an incorrect dose 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 2 weeks of maintenance treatment);
  - c) the regular daily buprenorphine dose is  $\leq 4$  mg, and the patient was incorrectly administered a dose of  $\geq 16$  mg.
  - d) a buprenorphine dose of  $\geq 64$  mg 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 is required the following day (in effect, a two-day dose has been administered), or no dose.

## 5.5 Diversion of buprenorphine

**Easily diverted.** As buprenorphine is a sublingual tablet, it can easily be diverted by patients. They may try to avoid taking their buprenorphine as directed, at the pharmacy, for the following reasons:

- 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.

**There are potential risks associated with these practices.**

1. Patients not taking their full dose of buprenorphine may be more likely to use heroin.
2. Injection of buprenorphine is associated with risks of venous thrombosis, thrombophlebitis and other local infections; and of systemic fungal or bacterial infections (particularly in circumstances where patients inject buprenorphine that has already been in their mouth).
3. Diversion of the medication to other people can result in overdose (through combination with other sedating drugs) or precipitation of withdrawal (e.g. when taken by a patient on a high dose of methadone).

**To minimise the risks of diversion, the following safeguards are recommended:**

- Pharmacists should note carefully whether the full number of buprenorphine tablets have been taken sublingually by the patient, who should not be allowed to handle the tablets prior to dosing.
- Pharmacists (or their assistants) should supervise the patient closely until the tablets have dissolved (about 3 - 7 minutes). However, inevitably there will be times when this is just not possible.

**In circumstances where diversion of buprenorphine is a possibility (for example, where there is inadequate time for supervision), the following strategies are recommended.**

- The pharmacist and medical practitioner should warn the patient of the potential health risks associated with misuse of the medication.
- The pharmacist should crush the tablets, administering a fine powder sublingually to reduce the time required for absorption and the potential for medication to be removed from the patient's mouth. While the effect of crushing tablets on the bioavailability of the sublingual preparation has not been examined, it is thought to have little clinical impact.

**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.**

## **5.6 Investigations**

**Urine testing:** Urine tests reveal someone's drug use in the preceding 48 - 72 hour period. This is an expensive investigation and should be conducted only if the results are likely to be important.

At the time of writing, Australian pathology laboratories do not routinely test for buprenorphine in the urine, and it will not be detected as an opioid.

The only possible indications for buprenorphine urine screening are:

- to confirm whether a patient has taken the take-away doses;
- to see if a patient (not in treatment) is abusing buprenorphine;

## **5.7 Analgesia requirements for patients on buprenorphine**

Patients maintained on buprenorphine will have a diminished response to opioids prescribed for analgesia. This is because of the 'blocking' effect of the buprenorphine on full opioid agonists. Consequently, patients on buprenorphine who suffer severe or chronic pain will require considerably higher doses of opioid analgesia than individuals not in buprenorphine treatment.

**The principles of analgesic management are:**

1. Use non-opioid analgesics where possible (such as aspirin, NSAIDs, paracetamol).

2. Maintain buprenorphine dose if acute or subacute analgesia is required. A temporary increase in buprenorphine dose may provide additional analgesic cover. *Patients who develop chronic pain which is not responding to buprenorphine, and who require ongoing additional analgesia, may require transfer to methadone treatment.*
3. Where additional opioid analgesia is required, the dose of opioid (eg morphine) should be clinically titrated according to clinical response. The dose of analgesic should be closely monitored if buprenorphine is reduced or stopped. The concern is that high morphine doses will be required while buprenorphine is exerting ‘blockade’ effects, but as the buprenorphine levels reduce (with a corresponding reduction in the ‘blocking’ effects of buprenorphine), there is the potential for over-sedation - or even overdose - from the high morphine doses. If buprenorphine treatment stops completely (eg due to the hospital pharmacy not having the drug, doctor ignorance or patient non-cooperation), the dose of morphine needs to be closely monitored every day for at least 4 - 5 days after the last buprenorphine dose. It will probably have to be reduced over time, to avoid an overdose.

## 5.8 Pregnancy and lactation

Inadequate research has been conducted on the effects of buprenorphine during pregnancy and lactation in humans. For this reason, and because of certain adverse effects reported in animal trials, buprenorphine is contra-indicated for both pregnant and lactating women.

<b>BUPRENORPHINE IS CONTRA-INDICATED FOR PREGNANT AND BREASTFEEDING WOMEN</b>
---

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

ADEC states that this group of drugs “has caused, or may be suspected of causing, harmful effects on the human fetus 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.

Any woman patient seeking maintenance 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.

<p>Women wanting to become pregnant are better advised to consider methadone maintenance, or alternative forms of treatment for the management of their heroin dependence.</p>
--

Reliable forms of contraception should be recommended to women *not* wishing to become pregnant.

### **The pregnant heroin user not in treatment**

Heroin-dependent women who become pregnant should be advised to commence maintenance substitution treatment, with methadone the preferred option.

### **The patient who becomes pregnant while in buprenorphine treatment.**

If this happens, advice should be sought from a specialist multi-disciplinary unit providing obstetric and paediatric services for chemically-dependent women and their babies. Counselling should be provided regarding treatment options, and support offered when a choice of action is made.

- **The continuation of pregnancy and transfer to methadone maintenance treatment.** This is the preferred option for the woman who wishes to continue with her pregnancy. She should be admitted to hospital for transfer to methadone, allowing for close observation of both her and the fetus, for evidence of withdrawal or distress.
- **The continuation of pregnancy and continuation of buprenorphine treatment.** In rare circumstances, discontinuation of buprenorphine treatment may pose a greater risk to mother and baby than continuing. In particular, the woman who refuses to transfer to methadone should be given the option of continuing her buprenorphine treatment after the risks to the foetus and baby and the concerns about breast-feeding whilst in buprenorphine treatment (see below), have been explained to her. The woman must be capable of giving informed consent.
- **Termination of pregnancy.** Women wishing to terminate the pregnancy should be referred to appropriate services.

### **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 will be required to monitor for developmental abnormalities.

### **Breast-feeding**

The effects of buprenorphine on infants of nursing mothers have not been well studied. For this reason, at this stage, buprenorphine treatment is contra-indicated for breast-feeding mothers.

## **SECTION 6. WRITING PRESCRIPTIONS & DISPENSING BUPRENORPHINE**

Buprenorphine is an opioid and is registered as an S8 medication. Special precautions should be taken by clinicians in the prescribing, handling, dispensing and storage of the medication.

### **6.1 Writing Prescriptions**

Prescriptions for buprenorphine may be on a standard prescription form. A valid prescription must specify the following:

- the name and address of the prescribing doctor who has been issued with the permit to prescribe;
- the patient's name and address;
- the date of the prescription;
- the preparation to be dispensed (buprenorphine 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), specifying the days of the week the patient is to be dosed;
- the beginning and end dates of the prescription.

**It is strongly recommended that the name of the pharmacy be included on the prescription.**

### **6.2 Protocols for administering buprenorphine**

#### **Procedures prior to dosing**

**Staff authorised to administer buprenorphine include a pharmacist, a medical practitioner or two registered nurses.**

**Prior to administering the medication, staff must:-**

- Establish the identity of the patient;
- Confirm that the patient is not intoxicated;
- Check currency and amount of 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;
- Record the dose in the Drug of Addiction recording system.

## **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 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 tablets have dissolved (3 - 5 minutes on average);
  - do not swallow the tablets (buprenorphine tablets have approximately half the bioavailability when taken orally compared to sublingually);
  - once the tablets are given to you they are your responsibility and will not be replaced.
3. Give the cup to the patient and ask the patient to tip the contents under the tongue. Discourage patients from handling tablets.
4. Observe the patient until you are satisfied tablets are not divertable (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.
5. Patients should sign that they have received their dose. Offer cordial or water to rinse taste out of mouth.
6. The prescriber should be notified if the pharmacist has concerns that patients may be attempting to divert their medication (see Section 5.5).

## **APPENDIX 1**

### **CLINICAL GUIDELINES FOR THE USE OF BUPRENORPHINE IN THE TREATMENT OF HEROIN DEPENDENCE**

Abbreviated Version

These guidelines have been prepared to aid medical practitioners in the selection and management of patients seeking treatment with buprenorphine for heroin dependence.

These guidelines were prepared under the auspices of the National Expert Advisory Committee on Illicit Drugs (NEACID) in collaboration with the National Evaluation of Pharmacotherapies for Opioid Dependence (NEPOD) project, the Royal Australian College of General Practitioners (RACGP) and the Australian Professional Society on Alcohol and Other Drugs (APSAD), and are funded by the Commonwealth Department of Health and Aged Care.

These guidelines are based on international research literature and clinical experience with the use of buprenorphine in Australia. These guidelines have undergone a rigorous process of review and have been formally endorsed by the RACGP and APSAD.

The contribution of various individuals and organisations in the drafting and review process is gratefully acknowledged.

The sublingual buprenorphine preparation, Subutex®, is registered for treating heroin dependence in Australia. Subutex® contains buprenorphine hydrochloride, is available in 0.4, 2, and 8 mg strength tablets; and is registered for maintenance and withdrawal treatment.

## 1. Clinical Pharmacology

Buprenorphine is a synthetic opioid derived from the morphine alkaloid thebaine. It is a *partial opioid agonist* with low intrinsic activity and high affinity at  $\mu$  opioid receptors.

### **It is effective in the treatment of heroin dependence because**

- **it substitutes for heroin**, preventing the emergence of opioid withdrawal symptoms and reducing cravings;
- **it diminishes the effects of additional opioids** (e.g. heroin) due to a high affinity for  $\mu$  receptors;
- **it is long-acting**, allowing daily (or less than daily) dosing. The duration of action is related to the buprenorphine dose administered: low doses (e.g. 2 mg) exert effects for up to 12 hours; higher doses (eg 16 - 32 mg) exert effects for as long as 48 - 72 hours.

Other relevant properties:

- **Peak clinical effects** are achieved 1 - 4 hours after sublingual administration.
- **Elimination half-life** is between 24 and 37 hours.
- **Metabolised** principally in the liver by glucuronide conjugation and N-dealkylation.
- **Excreted** principally in the faeces and urine.

### **Withdrawal syndrome from buprenorphine.**

Withdrawal on stopping treatment is milder than with other opioids (e.g. morphine). Typically, withdrawal from maintenance buprenorphine emerges 2 – 5 days after the last dose, with some features lasting up to several weeks.

### **Side effects:**

- Similar to other opioids, the most common being constipation, disturbed sleep, drowsiness, sweating, headaches and nausea.
- Most prevalent in the initial treatment period.
- High doses well-tolerated - rarely induce clinically-significant respiratory depression, even in individuals with low tolerance to opioids.

### **Drug Interactions:**

- **Other sedatives.** Buprenorphine in combination with other sedative drugs (e.g. alcohol, benzodiazepines) can result in respiratory sedation, coma and death.
- **Opioid antagonists.** Naltrexone can precipitate opioid withdrawal in patients on buprenorphine. Very high doses of naloxone (e.g. 10 - 35 mg) are required to reverse buprenorphine effects. As buprenorphine is not readily reversed by naloxone, in cases where buprenorphine is contributing to respiratory depression, ventilatory support will often be required.
- **Opioid agonists.** Buprenorphine exerts a degree of blockade on the effects of full agonist opioids, potentially complicating the use of opioids for analgesia. The initial dose of

buprenorphine can precipitate opioid withdrawal in patients with high levels of opioid use (e.g. recent and heavy heroin use, methadone transfers).

## 2. Regulatory requirements

Buprenorphine is an S8 medication.

- **A medical practitioner must be approved by the Department of Human Services to prescribe it.**
- **A prescribing doctor must hold a permit from the Department of Human Services for each client being treated.**

**Victorian administrative arrangements (such as arrangements for your absence, prescription writing, documentation to pharmacist, interim treatment without a permit, transfers) and policy are the same as for methadone (refer to the *Methadone Guidelines for Prescribers and Pharmacists*)**

## 3. Indications, contra-indications, precautions

**A comprehensive assessment by an authorised prescribing doctor is essential.**

*Indications:* Buprenorphine treatment is indicated for individuals only when the following criteria have been established:

- opioid-dependent;
- 18 years of age or more. (a second or specialist opinion should be sought for individuals under 18);
- able to provide proof of identity (required for treatment with all S8 medications);
- able to give informed consent to treatment.

*Precautions:* Particular caution should be exercised in prescribing for clients in the following circumstances:

- in high-risk polydrug use;
- with chronic pain;
- with concomitant severe psychiatric condition;
- in methadone maintenance on high doses (>30 mg);
- with sensitivity to buprenorphine;
- with concomitant medical conditions.

(As with all opioids, caution should be used in the case of recent head injury; acute abdominal conditions and severe respiratory, hepatic or renal disease).

*Contraindications:*

Those who showed severe side-effects to buprenorphine from previous exposure;

Pregnant women and breast-feeding mothers.

Severe respiratory or hepatic insufficiency

## 4. Prescribing guidelines for maintenance treatment

### Initial buprenorphine dose: inducting heroin users

*The first dose of buprenorphine should be administered at least 6 hours after the last heroin use to reduce the risk of precipitated opioid withdrawal.*

*The initial dose should be between 2 and 8 mg.*

The following must be taken into consideration when considering the initial dose:

- the degree of neuroadaptation (or tolerance) to opioids:
  - low or uncertain tolerance to opioids: 2 or 4 mg.
  - high levels of tolerance: 6 or 8 mg.
- extent of opioid withdrawal experienced by client at time of first buprenorphine dose:
  - moderate to severe opioid withdrawal: 6 to 8 mg.
  - little or no opioid withdrawal: 2 or 4 mg, or delay initial dose.
- perceived likelihood of continued alcohol, sedative drug (particularly benzodiazepines), or illicit heroin use warrants low initial buprenorphine doses, with frequent reviews.
- concurrent medical conditions may warrant the use of lower initial doses (see *Precautions*).

### Initial buprenorphine dose: transferring from methadone maintenance treatment

Clients transferring from methadone programs may experience precipitated withdrawal on commencing buprenorphine, and a proportion will continue to describe mild withdrawal features or dysphoria for 1 - 2 weeks after the transition. The key factors impacting upon precipitated withdrawal are described below.

Factor	Discussion	Recommended strategy
Dose of methadone	Methadone doses higher than 30 mg are more often associated with precipitated withdrawal. In general the higher the methadone dose, the more severe the withdrawal experienced.	Attempt transfer from low dose of methadone (e.g. < 40 mg where possible). Clients on > 60 mg methadone should not attempt transfer
Time between last methadone dose and 1 <sup>st</sup> dose buprenorphine	Buprenorphine should not be dispensed within 24 hrs of last methadone dose. Increasing the interval between last methadone and 1 <sup>st</sup> buprenorphine dose reduces the incidence & severity of precipitated withdrawal	Cease methadone and delay first dose of buprenorphine until client experiencing features of methadone withdrawal
Dose of buprenorphine	Very low doses of buprenorphine (e.g. 2 mg) are generally inadequate to substitute for methadone (unless very low methadone dose). High first doses of buprenorphine (e.g. 8 mg or more) are more likely to precipitate withdrawal.	First dose of buprenorphine should generally be 4 mg; review client 2 - 4 hours later (or early the following day if evening dose)
Client expectancy	Clients who are not prepared for precipitated withdrawal are more likely to be distressed and confused by its onset, with potential negative consequences (e.g. treatment drop-out, drug abuse).	Inform clients fully (and carers where relevant). Provide written information. Have contingency plan in place for severe symptoms.
Use of other medications	Symptomatic medication (e.g. clonidine) can be useful to relieve any precipitated withdrawal.	Prescribe and dispense in accordance to management plan

## Transferring clients from low methadone doses (<40mg)

Methadone dose should be ceased abruptly, and the first buprenorphine dose given at least 24 hours after the last methadone dose. The following conversion rates should be used when converting from low-dose methadone to buprenorphine.

Last methadone dose (mg)	Initial buprenorphine dose (mg)	Day 2 buprenorphine dose (mg)
20 - 40 mg	4 mg	6 - 8 mg
10 - 20 mg	4 mg	4 - 8 mg
1 - 10 mg	2 mg	4 mg

## Transferring from medium dose methadone (40 - 60 mg) to buprenorphine

Clients who are unable to reduce their methadone dose to below 40 mg without becoming 'unstable' may attempt a transfer from methadone doses between 40 and 60 mg. The following procedures should be followed:

1. Prepare client, pharmacist and other staff. Provide information and organise supports.
2. Cease methadone dose and delay first buprenorphine dose until the client experiences significant withdrawal discomfort (generally 48 - 96 hours after last methadone dose). Symptomatic medication (limited amounts) may be required.
3. Give the first dose of 4 mg buprenorphine in the morning or early afternoon.
4. Review the client 2 - 4 hours after first buprenorphine dose. If client describes:
  - worsening of withdrawal following first buprenorphine dose - provide symptomatic medication for opioid withdrawal for remainder of the day.
  - no worsening of withdrawal, or an improvement in withdrawal symptoms following the first buprenorphine dose - a further 2 to 4 mg of buprenorphine can be dispensed that afternoon / evening.
5. Review the client prior to dosing the following day. Titrate the dose to between 6 -10 mg, according to the response on the previous day. Continue frequent reviews and dose titration.

## Stabilisation

The key principles to stabilising clients are:

- frequent review of the client by the prescribing doctor and other members of the treatment team;
- increases in buprenorphine dose only after review by the prescribing doctor;
- titration of the buprenorphine dose according to:
  - features of intoxication, withdrawal and cravings over preceding 24 hours;
  - additional drug-use (eg heroin), including the reason stated by the client for using;
  - side-effects or other adverse events (including intoxicated presentations, overdoses);
  - adherence to dosing regime (attendance for dosing, route of administration);
  - client satisfaction with buprenorphine dose.
- dose changes:
  - increases should be by increments of 2 - 4 mg at a time;

- allow at least 2 - 3 days between dose increases, although daily increases are possible.

Clients should generally be able to achieve maintenance buprenorphine dose levels within 1 to 2 weeks of commencing buprenorphine. Daily dosing is recommended during the stabilisation period.

### **Maintenance treatment**

Evidence suggests that most people achieve optimal outcomes on daily doses of 12 - 24 mg. The maximum recommended dose of buprenorphine is 32 mg daily.

### **Frequency of dosing**

Most clients can be maintained on doses of buprenorphine administered every 2 or 3 days. The following conversion is recommended:

2-day buprenorphine dose = 2 x daily dose of buprenorphine (to a maximum of 32 mg)

3-day buprenorphine dose = 3 x daily dose of buprenorphine (to a maximum of 32 mg)

This conversion serves as a guide only, and the dose should be titrated according to clinical response. A proportion of clients (10-20%) do not tolerate alternate or three-day dosing.

## **Ancillary services / interventions**

### **Psychosocial services:**

All clients should be encouraged to join a comprehensive treatment program that includes psychosocial services such as counselling. However, attending counselling should be voluntary.

### **Take-away doses:**

The take-away policy for buprenorphine is determined by each Australian jurisdiction. There are both benefits and problems associated with take-aways, and particular care should be exercised by prescribers in authorising them.

### **Urine-testing:**

Buprenorphine is not detected in routine urine tests for opioids.

### **Addressing continued high-risk drug use:**

Attempts should be made to stabilise clients who continue high-risk heroin or other drug-use (as evidenced by frequent intoxicated presentations, overdoses, chaotic drug-related behaviours, or drug-related deterioration of medical or mental health).

This requires a review of:

- (a) psychosocial interventions and supports;
- (b) precipitants to continued drug use; *and*
- (c) medication regimes.

Ensure an adequate dose of buprenorphine is prescribed **and** that the client is taking it as prescribed (which may require stopping take-away doses, supervising consumption, and imposing daily dosing regimes).

Clients who cannot stabilise on buprenorphine should consider transferring to an alternative pharmacotherapy (e.g. methadone); or consider non-pharmacological treatment options (e.g. therapeutic communities, counselling and support) and withdrawal from substitution maintenance treatment.

### **Cessation of buprenorphine maintenance treatment**

Withdrawal from buprenorphine treatment

Most clients do not experience significant withdrawal discomfort until they reduce to low doses of buprenorphine, or even until after doses have stopped (see pharmacology for description). A gradual dose reduction is proposed at the following rate:

Daily buprenorphine dose	Reduction rate
Above 16 mg	4 mg every 1 – 2 weeks
8 - 16 mg	2 to 4 mg every 1 – 2 weeks
Below 8 mg	2 mg per week or fortnight

Some clients will request doses of less than 2 mg. An increase in heroin or other drug-use, or a worsening of the client's physical, psychological or social well-being, may warrant a temporary cessation or slowing-down of the reduction rate.

Induction on to naltrexone

Some clients may wish to commence naltrexone as a relapse-prevention agent following buprenorphine maintenance treatment. Induction on to naltrexone at least 5 - 7 days after the last buprenorphine dose is generally possible with minimal discomfort. Naltrexone can be commenced more quickly (within several days of ceasing buprenorphine), but this has attendant risks, and the reader is referred to the more comprehensive guidelines for recommendations.

Transfer to methadone maintenance treatment

Clients should be stabilised on daily doses of buprenorphine prior to transferring to methadone. *Methadone can be commenced 24 hours after the last dose of buprenorphine, at an initial maximum daily dose of up to 40mg.* Clients transferring from low doses of buprenorphine (eg 4 mg or less) should be commenced on lower methadone doses (e.g. <20 mg). The client should be reviewed frequently, and the methadone dose titrated accordingly.

## **5. Guidelines for the management of heroin withdrawal**

**The non-pharmacological management of heroin withdrawal should include:**

- *Assessment and treatment selection;*

- *Environment and support management*: involving family, friends, alcohol & drug workers, self-help and peer groups;
- *Supportive care* (including provision of information and supportive counselling);
- *Monitoring* (use of withdrawal scales and daily review is recommended);
- *links to post withdrawal services*.

### Prescribing and administering buprenorphine for withdrawal

- Delay first dose until at least 6 hours after last heroin use, and preferably until the client is experiencing early features of opioid withdrawal.
- Dispense daily, with daily clinical review.
- Titrate doses against the client's experience of withdrawal severity, cravings, side-effects and other drug use.

#### *Outpatient withdrawal regimes*

The following 4 - 8 day dosing regime is proposed for outpatient withdrawal services:

Day	Proposed regime	Recommended upper and lower limits
Day 1	6 mg	4 – 8 mg
Day 2	8 mg	4 – 12 mg
Day 3	10 mg	4 – 16 mg
Day 4	8 mg	2 – 12 mg
Day 5	4 mg	0 – 8 mg
Day 6	-	0 – 4 mg
Day 7	-	0 – 2 mg
Day 8	-	0 – 1 mg

Clients who do not stop their heroin use during their outpatient withdrawal episode may benefit from:

- an extension of the outpatient buprenorphine withdrawal regime over several weeks;
- transfer to inpatient withdrawal services; *or*
- transfer to longer-term maintenance programs.

#### *Inpatient withdrawal regimes*

*Modify inpatient regimes according to:*

- the duration of the withdrawal episode, and
- degree of monitoring and supervision available.

Regime proposed for a 7 - 8 day admission.

Day	Proposed regime	Total daily dose
Day 1	4 mg at onset of withdrawal, & additional 2 to 4 mg evening dose prn	4 - 8 mg
Day 2	4 mg mane, with additional 2 to 4 mg evening dose prn	4 - 8 mg
Day 3	4 mg mane, with additional 2 mg evening dose prn	4 - 6 mg
Day 4	2 mg mane prn; 2 mg evening prn	0 - 4 mg
Day 5	2 mg prn	0 - 2 mg
Day 6	no dose	

**Ancillary medications:** Because buprenorphine is effective in reducing most withdrawal symptoms, other withdrawal medications are not routinely required. Some clients may complain of sleep disturbance, but only limited amounts of benzodiazepines should be prescribed (e.g. temazepam 10 - 20 mg nocte for two nights), with supervised dispensing. *The use of high doses of benzodiazepines in combination with buprenorphine can result in overdose.*

**Post-withdrawal treatment options:** Withdrawal alone has limited long-term benefits, and all clients attempting withdrawal should be encouraged to pursue ongoing drug treatment.

*Options open to them include:*

- counselling services,
- substitution maintenance treatment (with methadone or buprenorphine),
- naltrexone treatment,
- self-help groups (e.g. Narcotics Anonymous), *or*
- residential rehabilitation programs.

## APPENDIX 2

### THE SUBJECTIVE OPIATE WITHDRAWAL SCALE (SOWS)

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

Range 0-64. Handelsman, L., Cochrane, K. J., Aronson, M. J. et al. (1987)

Two New Rating Scales for Opiate Withdrawal, *American Journal of Alcohol Abuse*, 13, 293-308.

## OBJECTIVE OPIOID WITHDRAWAL SCALE (OOWS)

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

Range 0-13 Handelsman, L., Cochrane, K. J., Aronson, M. J. et al. (1987) Two New Rating Scales for Opiate Withdrawal, American Journal of Alcohol Abuse, 13, 293-308.

## APPENDIX 3

### CLINICAL AND SUPPORT SERVICES

#### **Victorian Drug and Alcohol Clinical Advisory Service (DACAS)**

Exclusively for health and welfare professionals. Provides advice and information on clinical management of patients with drug and or alcohol problems, including:

- advice on recognition and management of withdrawal syndromes
- drug use complications
- drug information
- prescribing information
- assistance with cases of acute intoxication

Contact details

Metropolitan: 03 9416 3611

country areas (toll free): 1800 81 2804

#### **Drugs and Poisons Unit, Department of Human Services**

The Unit issues permits for approved practitioners to prescribe methadone. It also approves individual medical practitioners and pharmacists to respectively prescribe or dispense methadone.

Contact details:

Address: PO Box 1670N, MELBOURNE 3001

phone: 1300 364 545

fax: 1300 360 830

#### **Direct Line**

For the general public and health and welfare professionals. Provides counselling, information and referral, including:

- needle syringe exchange and bin location
- drug and alcohol agencies and drug withdrawal beds
- methadone program contact details
- HIV/AIDS information and referral
- drink/drive education and assessment referral

contact details

Metropolitan: 03 9416 1818

country areas (toll free): 1800 13 6385

#### **Youth Substance Abuse Service**

YSAS 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.

14-18 Brunswick Street, FITZROY 3065

Phone: 03 9415 8881

FAX: 03 9415 8882

website: <http://www.ysas.org.au>

### **YSASLine**

YSASline provides 24 hour access to information, telephone counseling, and referral to YSAS outreach teams. The service is open to young people, their families, health and welfare workers, police and ambulance officers. Call YSASline to contact an outreach team. Access to the YSAS residential service is made by contacting your local outreach team via YSASline.

metro: 03 9244 2450

country freecall: 1800 014 446

### **VIVAIDS: the Victorian Users Group**

765a Nicholson Street NORTH CARLTON 3054

Phone: 03 9381 2211

VIVAIDS provides information on anything and everything to do with drugs. They also provide peer support, peer education, referrals, needle exchange and advocacy to drug users, while promoting harm reduction to users and the community.

### **Specialist Methadone Services**

Specialist Methadone Services provide a consultative service to methadone prescribers seeking expert opinion about the management of patients with special problems, such as psychiatric, social, medical or treatment problems. Patients may be referred by arrangement, or advice sought by contacting the service.

### **Turning Point Drug and Alcohol Centre**

54 Gertrude St., FITZROY 3065

Administration Phone 03 9254 8061 Fax 03 9416 3420

Clinical Services Phone 03 9254 8050 Fax 03 9486 9766

### **South Eastern Methadone Consultancy Clinic**

61-69 Brighton Rd., ELWOOD 3184

Phone: 03 9525 7399 Fax: 03 9525 7369

### **Western Hospital Drug and Alcohol Service**

Gordon St., FOOTSCRAY 3011

Phone: 03 9317 2217 Fax: 03 9319 6027

### **Austin and Repatriation Medical Centre Specialist Methadone Service**

Studley Rd., HEIDELBERG 3084

Administration Phone: 03 9496 5000

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

### **Eastern Region Specialist Methadone Service**

Whitehorse Community Health Service

65 Carrington Road, BOX HILL Phone: 03 9890 2220

### **Royal Women's Hospital Chemical Dependency Unit**

264 Cardigan Street CARLTON 3053 Phone: 03 9344 2363

For women who are pregnant and use drugs. The unit provides a direct service for women who live within a 25 Km radius, and secondary consultation for other women. Midwives and social workers are available for consultation.

## **Health Insurance Commission.**

The HIC provides information about medical consultations and pharmaceutical benefits obtained through its Doctor Shopper Hotline. It is also able to provide this information if the patient signs a privacy release form authorising the HIC to provide this information. Forms and explanatory letters are available from the HIC.

Health Insurance Commission, 134 Reed Street, TUGGERANONG ACT 2900

Doctor shopper hotline (free call): Phone: 1800 631 181

## **Hepatitis C information**

### **Hepatitis C Support Line**

#### **Hepatitis C Council**

Level 9, Carlow House, 289 Flinders Lane, MELBOURNE 3000

Phone: 03 9639 3200

Country Calls: 1800 703 003

The Hepatitis C Council has produced a booklet "*Hepatitis C Contact*" which provides information, and answers frequently asked questions.

### **Hepatitis C Helpline**

Telephone: 03 9349 1111

Country Calls: 1800 800 241

TTY: 1800 032 665

Vietnamese Line: 1800 456 007

## **Department of Human Services.**

DHS pamphlet "*Hepatitis: the Facts*" available from the Department of Human Services, or on the internet at: <http://www.dhs.vic.gov.au/phd/9904043/index.htm>

The Department of Human Services has produced a booklet "*Management, Control and Prevention of Hepatitis C: Guidelines for Medical Practitioners*". It is available from the Department.

Health care providers can obtain information and assistance with counselling from the Hepatitis C Educator (03 9288 4127). Advice on notification of hepatitis C can be obtained from the Infectious Diseases Unit.

## **AIDS information**

### **AIDSLINE**

Phone: 03 9347 6099

Country Calls: 1800 133 392

TTY: 1800 032 665

### **Melbourne Sexual Health Centre**

580 Swanston Street, CARLTON 3053

Phone: 03 9347 0244

Country Calls: 1800 032 017

## **Needle and Syringe Exchange Programs (NSEPs).**

Contact details of Victorian NSEPs is available:

On the internet at: <http://hna.ffh.vic.gov.au/phb/9808109/index.htm>

or by calling Direct Line (see above).