

# 3

## Guidelines for maintenance treatment

### 3.1 Gateway model of treatment with buprenorphine

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

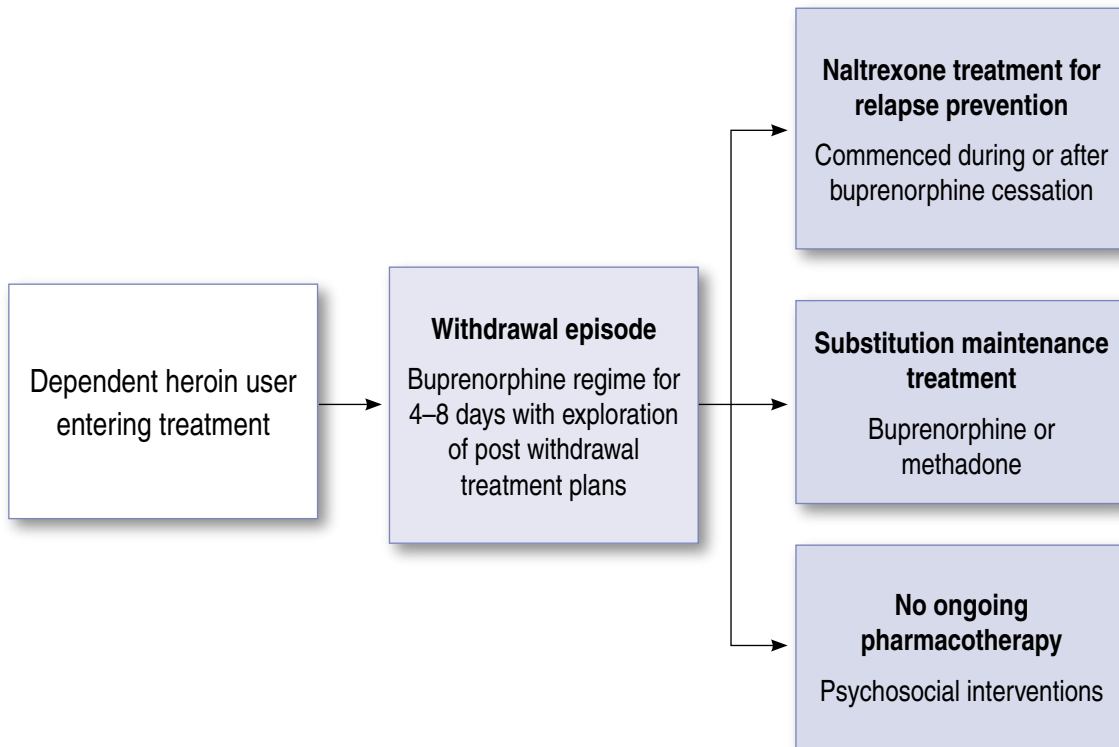
Clinical experience and research have repeatedly demonstrated that motivation to remain abstinent is often short-lived. There is strong evidence that longer-term treatment is associated with a greater likelihood of long-term abstinence from heroin than are shorter periods of treatment. Stability and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

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

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

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

**FIGURE 1. GATEWAY MODEL OF TREATMENT WITH BUPRENORPHINE**



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

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

## 3.2 Selecting maintenance pharmacotherapies

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

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

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

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

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

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

#### FACTORS TO CONSIDER WHEN SELECTING MAINTENANCE PHARMACOTHERAPIES

**Patient preference**

**Response to treatment**

**Individual variation in absorption, metabolism & clearance rates**

**Adverse effects**

**Logistics of participating in treatments**

**General expectations of the treatment**

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

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

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

## 3.3 Induction onto buprenorphine treatment

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

### 3.3.1 Commencing buprenorphine from heroin use

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

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

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

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

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

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

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

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

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

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

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

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

### 3.3.2 Transferring from methadone maintenance treatment

Transfer from methadone to buprenorphine may be appropriate when:

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

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

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

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

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

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

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

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

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

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

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

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

## Transferring from higher doses of methadone (>40mg)

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

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

## 3.4 Stabilisation

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

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

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

### TO ACHIEVE STABILISATION OF BUPRENORPHINE DOSE:

#### **Regular patient review for first few weeks**

*adequacy of dose; withdrawal symptoms, side-effects, any additional drug use*  
(see below for minimal schedule of prescriber reviews).

#### **Increase dose only as indicated by reviews**

(see below for guidance on titration of doses)

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

### 3.4.1 Regular patient review

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

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

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

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

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

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

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

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

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

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

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

## 3.4.2 Changes in buprenorphine dose

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

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

**TABLE 4: INDICATORS OF NEED FOR DOSE ADJUSTMENT**

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

## 3.5 Maintenance dosing

### 3.5.1 Dose levels

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

## 3.6 Unsupervised doses

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

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

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

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

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

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

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

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

## Indications of stable drug use

Drug use is assessed by:

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

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

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

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

## Risk assessment

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

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

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

## 3.7 Ancillary interventions

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

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

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

## 3.8 Continued high-risk drug use

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

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

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

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

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

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

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

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

## 3.9 Missed doses

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

The following procedures are recommended:

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

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

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

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

## 3.10 Cessation of buprenorphine maintenance treatment

### Nature of withdrawal from buprenorphine maintenance treatment

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

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

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

### Voluntary withdrawal from buprenorphine maintenance treatment

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

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

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

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

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

Contraindications to dose reduction and withdrawal include:

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

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

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

**TABLE 5: RATES OF DOSE REDUCTION**

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

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

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

## Supportive care

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

## Involuntary withdrawal

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

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

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

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

## Commencing naltrexone following buprenorphine maintenance treatment

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

The following procedures are recommended.

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

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

## Transferring to methadone

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

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

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

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

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