New Zealand Clinical Guidelines for the Use of Buprenorphine (with or without Naloxone) in the Treatment of Opioid Dependence
Foreword

These guidelines, *New Zealand Clinical Guidelines for the Use of Buprenorphine (with or without Naloxone) in the Treatment of Opioid Dependence*, provide a framework for the effective, safe and responsive delivery of opioid substitution treatment. They will be appended to *Opioid Substitution Treatment: New Zealand Practice Guidelines* (Ministry of Health 2008).

Similar to the national practice guidelines, these guidelines stress the key principles of safety, stabilisation, assessment and review, treatment planning, clinical case management and integrated treatment. They also emphasise the particular skills (both professional and personal) and knowledge that reinforce the need for a trained, well-informed and accountable opioid treatment workforce.

Clinicians may vary their practice from that stated in these guidelines (eg, in unforeseen circumstances), but must clearly document the reasons for such variation in the client’s records or in the service-delivery model documents. There should be no variation from the administrative and legislative requirements contained in *Practice Guidelines for Opioid Substitution Treatment in New Zealand* (Ministry of Health 2008).

Dr David Chaplow
Director of Mental Health
Acknowledgements

The Ministry of Health endorses these guidelines for use as the national standard for opioid treatment using buprenorphine (with or without naloxone). The guidelines were written on behalf of the opioid treatment sector by staff of Community Alcohol and Drugs Services (CADS), Auckland, in particular Carina Rundle, senior pharmacist, Andi Barrett, senior clinical pharmacist, and Dr Karla Rix-Trott, lead medical officer.

A range of practitioners from New Zealand and overseas and the National Association of Opioid Treatment Providers contributed to the guidelines. The growing literature related to opioid treatment using buprenorphine (with or without naloxone) also informed the guidelines.

The draft guidelines were reviewed by Associate Professor James Bell, University of New South Wales, Sydney, Australia.
Contents

Foreword iii

Overview 1
  Purpose of these guidelines 1
  Use of these guidelines with other guidelines 1
  Scope of these guidelines 1
  Audience for these guidelines 1
  Glossary 1
  Associated documents 1

Literature Review 3
  Properties of substitution medications 3
  Evidence for use 3
  Situation in New Zealand 3
  Buprenorphine compared with methadone 4
  Misuse of buprenorphine 7

Pharmacology 9
  Opioid receptors 9
  Full, partial and antagonist properties of the mu opioid receptor 9
  Pharmacology of buprenorphine alone 10
  Pharmacology of naloxone alone 11
  Pharmacology of buprenorphine in combination with naloxone (Suboxone®) 11
  Pharmacokinetics of buprenorphine alone 11
  Pharmacokinetics of naloxone alone 12
  Pharmacokinetics of buprenorphine with naloxone 13
  Contraindications and precautions for buprenorphine (with or without naloxone) 13
  Common side effects and adverse effects 14
  Drug interactions 15

General Information 17
  Formulation of Subutex® and Suboxone® 17
  Controlled drug classification of Suboxone® 17

Induction on to Buprenorphine (with or without Naloxone) 18
  Pharmacotherapy selection 18
  Precipitated withdrawal 20
  Transfer from street drugs (illicit opioid use) 21
  Transfer from methadone substitution treatment 25

Buprenorphine (with or without Naloxone) Substitution 29
  Stabilisation period 29
  Substitution treatment 29
New Zealand Clinical Guidelines for the Use of Buprenorphine (with or without Naloxone) in the Treatment of Opioid Dependence
Appendices

Appendix A: Drug Interactions with Buprenorphine (with or without Naloxone) 66
Appendix B: Medications to Relieve the Symptoms of Opioid Withdrawal 69
Appendix C: Information for Clients 70

List of Tables

Table 1: Associated and reference documents 2
Table 2: Effect of misuse of buprenorphine (with and without naloxone) 7
Table 3: Summary of pharmacokinetics of buprenorphine alone 12
Table 4: Very common adverse events reported by at least 10 percent of subjects 15
Table 5: Common adverse events reported by at least 1 percent of subjects 15
Table 6: Schedule 1: Buprenorphine (with or without naloxone) doses for the first three days of treatment 23
Table 7: Schedule 2: Buprenorphine (with or without naloxone) doses for the first three days of treatment 23
Table 8: Summary of procedure for prescribers transferring a client from illicit drugs 24
Table 9: Conversion rates for low-dose methadone transfer 26
Table 10: Summary of procedure for transferring a client from methadone substitution treatment 28
Table 11: Increase in buprenorphine (with or without naloxone) after first dose 29
Table 12: Conversion of a daily dose of sublingual buprenorphine (with or without naloxone) to a less-than-daily dose 32
Table 13: Recommended recommencement doses of buprenorphine (with or without naloxone) 34
Table 14: First methadone dose after transfer from buprenorphine (with or without naloxone) 35
Table 15: Dose reduction rates when reducing from buprenorphine (with or without naloxone) 35
Table 16: Gradual dose taper schedule of buprenorphine (with or without naloxone) 36
Table 17: Process to minimise the risk of diversion or misuse 38
Table 18: Suggested transfer schedule from buprenorphine (with or without naloxone) to methadone 43
Table 19: Fixed dosing schedules for buprenorphine (with or without naloxone) withdrawal in an inpatient setting 54
Table 20: Flexible dosing schedule for buprenorphine (with or without naloxone) withdrawal in an inpatient setting 55
Table 21: Example of outpatient withdrawal regimen, recommended upper and lower limits of buprenorphine (with or without naloxone) 56
Table 22: Example of 20 to 36 day outpatient withdrawal regimen from buprenorphine (with or without naloxone) 56
Table 23: Medications metabolised by cytochrome P450 3A4 67
Table 24: Medications to relieve symptoms of opioid withdrawal 69

List of Figures

Figure 1: Effect of three types of opioid with an affinity for the mu receptor 10
Figure 2: Severity of withdrawal over time 21
Overview

Purpose of these guidelines
These guidelines state the best practice for prescribing, and provide guidance on the use of, buprenorphine alone or in combination with naloxone for managing opioid dependence.

Use of these guidelines with other guidelines
These guidelines are to be used in conjunction with Practice Guidelines for Opioid Substitution Treatment in New Zealand (Ministry of Health 2008) and local service protocols and procedures.

Note: Buprenorphine is available as two tablet preparations:
- alone (Subutex®)
- with naloxone (Suboxone®).

These guidelines cover both preparations, although only Suboxone® is currently registered in New Zealand.

Scope of these guidelines
These guidelines cover induction, maintenance and withdrawal using buprenorphine, and discuss the pharmacology and pharmacokinetics of buprenorphine and naloxone.

Audience for these guidelines
People involved with the prescribing, dispensing and administration of buprenorphine for opioid substitution treatment are the main audience for these guidelines.

Glossary
Many of the technical words and phrases used in these guidelines are defined in the Glossary, page 62.

Associated documents
Table 1 lists the documents closely associated with or referenced in these guidelines.
Table 1: Associated and reference documents

<table>
<thead>
<tr>
<th>Type</th>
<th>Title or description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guidelines</td>
<td><em>Practice Guidelines for Opioid Substitution Treatment in New Zealand</em> (Ministry of Health 2008).</td>
</tr>
</tbody>
</table>

New Zealand Clinical Guidelines for the Use of Buprenorphine (with or without Naloxone) in the Treatment of Opioid Dependence
Literature Review

Properties of substitution medications
A substitution medication for opioid dependence should (WHO 2004):

- have opioid properties providing the capacity to prevent emergence of withdrawal symptoms (cross-tolerance)
- reduce craving
- diminish the effects of heroin or other opioid drugs due to binding at opioid receptors in the brain
- have a longer duration of action than the drug it is replacing, thereby delaying the emergence of opioid withdrawal and decreasing how often it needs to be administered
- be administered orally
- be able to be prescribed in decreasing doses for detoxification purposes.

Evidence for use
Buprenorphine is increasingly considered an alternative to methadone in the treatment of opioid dependence for both substitution and detoxification (Tzschentke 2002). It has the advantage of containing the properties of an ‘ideal’ substitution medication.

Tolerance to the repeated administration of opioid drugs is widely known. This is an advantage when treating drug dependency, because opioid substitution treatments provide cross-tolerance to illicit opioid drugs (Walsh and Eissenberg 2003). Buprenorphine alleviates opioid withdrawal symptoms and cravings (Raisch et al 2002) while helping to reduce illicit use by reducing the positive effects from ‘use on top’.

The effect of buprenorphine to reduce illicit ‘use on top’ may occur in two ways: cross-tolerance and pharmacological antagonism (Walsh and Eissenberg 2003).

Repeated administration of buprenorphine produces or maintains opioid dependence. The physical dependence liability is milder than that with methadone or heroin (Raisch et al 2002). Evidence of this is that even after the prolonged use of buprenorphine, spontaneous withdrawal symptoms and naloxone-precipitated withdrawal symptoms tend to be relatively moderate compared with those of other opioids such as methadone (Tzschentke 2002).

Situation in New Zealand
New Zealand is in a unique situation compared with the rest of the world, because it has not had a large heroin problem for many years. Physical dependence on opioid drugs is usually because of a person’s misuse of products such as:

- long-acting morphine tablets (ground tablets that are chemically treated or ‘turned’ with acetic anhydride into an injectable morphine/diamorphine mix)
- illicit methadone
- poppy-seed tea
- homebake (‘turned’ codeine that forms a morphine/diamorphine mix).

People tend to develop and maintain their opioid dependence by using over-the-counter products (such as Gees Linctus (a type of cough mixture) or products containing codeine) or prescribed medications such as pethidine, long-acting morphine and dextropropoxyphene, codeine or dihydrocodeine.

Most sources of opioids in New Zealand are pharmaceutical preparations, so the amount taken illicitly is equal to or less than the pharmaceutical preparation, depending on the skill of the person ‘turning’ the tablets. Therefore, the risk of overdose in New Zealand is relatively low compared with the risk in countries where heroin is the dominant opioid used.

Methadone-related deaths in New Zealand occur least often compared with deaths related to morphine and dextropropoxyphene (Reith et al 2005).

**Buprenorphine compared with methadone**

Clinical trials have compared the efficacy of buprenorphine to that of methadone in the outpatient treatment of people with opioid dependence. They have found that the use of buprenorphine results in treatment retention rates and opioid-positive urine samples that are comparable to those resulting from the use of methadone (Strain et al 1997).

Buprenorphine is used for short-term opioid detoxification or as an alternative substitution medication to methadone.

Buprenorphine alone (or with naloxone) provides opioid-dependent people with:
- a wider selection of treatment options for their opioid dependence, potentially targeting a new set of people who do not see methadone as a treatment option for themselves
- an alternative for people who have adverse side effects from methadone, including methadone-related Torsade de Pointes
- an alternative for detoxification from opioids
- an alternative for people who experience unpleasant effects from methadone
- a medication that is induced more rapidly than methadone
- a medication with a good safety profile (ie, a low risk of overdose) when not used in combination with other central nervous system (CNS) depressants.
Buprenorphine is a partial agonist

Buprenorphine, like methadone, produces opioid effects, thereby reducing a person’s craving for illicit opioids and enhancing treatment retention. However, methadone is a full opioid agonist, whilst buprenorphine is a partial agonist with a ‘ceiling’ on the amount of opioid effect produced.

Buprenorphine has the advantage of being less sedating than methadone (Chadderton 2000). Although the maximum opioid activity for buprenorphine is less than that from a full agonist, it is usually sufficient to suppress opioid-withdrawal effects (Chadderton 2000).

Buprenorphine can result in diminished illicit ‘use on top’

At sufficient doses, methadone alleviates opioid withdrawal and the need for additional illicit ‘use on top’. However, if illicit opioids are used, they will produce additional opioid effects if they are able to reach the receptor sites. Buprenorphine, with its high affinity for the opioid receptor sites blocks other opioids from the receptor site while it is present (Ling et al 1998). This reduces the potential for ‘use on top’, because no additional opioid effects will occur.

Buprenorphine has a long duration of action

Buprenorphine’s duration of action varies depending on the dose prescribed. Clinical effects peak one to four hours after taking a sublingual dose. At low doses (eg, 2 mg) effects will usually continue to be experienced for up to 12 hours, whilst at higher doses (eg, 16 to 32 mg) effects may last as long as 48 to 72 hours (Lintzeris et al 2006).

Buprenorphine can be prescribed on a less-than-daily dosing regimen

Buprenorphine’s long duration of action together with the ceiling dose response effect mean less-than-daily dosing regimens are effective. Clinical trials have shown that around 80 percent of clients can tolerate a less-than-daily dosing regimen.

Buprenorphine may have a milder withdrawal syndrome

There is limited evidence regarding buprenorphine withdrawal in terms of features and severity. Symptoms and signs of withdrawal are the same as those for other opioids. Buprenorphine differs from other opioids in that the onset of withdrawal after stopping is delayed and the withdrawal itself may be milder than that experienced with methadone, morphine or heroin (Lintzeris et al 2006).

Buprenorphine can be used at the end of a methadone-withdrawal programme and requires less adjunctive prescribing.

Buprenorphine also requires a shorter inpatient stay and a greater percentage of detoxifications can be on an outpatient basis, resulting in lower inpatient treatment costs. However, as with all opioid withdrawal regimens the rate of relapse is relatively high.
Buprenorphine is taken sublingually

The sublingual buprenorphine tablet requires more supervised consumption time at the pharmacy than does the liquid methadone formulation (Chadderton 2000). Alternate-day dosing may compensate for this extra time.

Tablets can also be more easily diverted than liquids, because of their longer absorption time.

Buprenorphine is safer in overdose

Buprenorphine has a better safety profile in overdose when not used in combination with other drugs than does methadone. This is due to the partial agonist effect that causes a ceiling-dose effect, a ceiling effect on respiratory depression (Strain et al 1997), and a bell-shaped curve in overdose where even fewer opioid effects occur than with a moderate dose (Johnson et al 2003b).

Low doses of buprenorphine have, however been found to be toxic when combined with other central nervous system depressants such as benzodiazepines and alcohol (Lintzeris et al 2006).

Because the sublingual preparation is poorly absorbed orally, buprenorphine is safer than other opioids in accidental overdose (eg, children) where the tablets have been swallowed.

Buprenorphine's side-effect profile is similar to that of other opioid drugs

Like methadone, buprenorphine is an opioid medication, so has opioid side effects. Compared with methadone, buprenorphine causes less sweating, constipation and sedation, but severe headaches are occasionally reported (Chadderton 2000). Moderate headaches with buprenorphine are common during the first few days of induction. Buprenorphine, however, can induce precipitated withdrawal at induction.

Buprenorphine produces less neonatal abstinence syndrome

Buprenorphine appears to reduce the severity of neonatal abstinence syndrome (NAS) compared with methadone (Fischer et al 2000), but this is not firmly established and NAS does occur. *Buprenorphine is unlicensed for use in pregnancy.*

Reduction of cross-tolerance effect

The plateau caused by the ceiling effect of buprenorphine means some clients may not be able to stabilise on buprenorphine as increased dosages may not produce further clinical improvements (Strain et al 1997).
Misuse of buprenorphine

Studies from France (where buprenorphine (without naloxone) treatment for opioid dependence has been available from 1996) report that buprenorphine is subject to injecting misuse (Guichard 2003; Obadia et al 2001). This has also occurred in other countries (Strain et al 1997), including New Zealand (Robinson et al 1993).

Research has evaluated different formulations of buprenorphine (with or without naloxone) and found that buprenorphine in combination with naloxone appears to decrease the potential for misuse (Mendelson and Jones 2003; Stoller et al 2001). However, it has been found that the ratio of buprenorphine to naloxone in the preparation is important. A ratio of 4 : 1 buprenorphine to naloxone is the most effective for deterring misuse and maintaining a therapeutic effect (Chiang and Hawks, 2003; Ling 2001, Mendelson et al 1999).

If an opioid-dependent person misuses buprenorphine (with or without naloxone), the effect will depend on their level of physical dependence and the time between their last opioid dose and first buprenorphine dose (see Table 2).

Table 2: Effect of misuse of buprenorphine (with and without naloxone)

<table>
<thead>
<tr>
<th>Physical status</th>
<th>Sublingual buprenorphine with naloxone</th>
<th>Intravenous buprenorphine with naloxone</th>
<th>Intravenous buprenorphine alone (eg, Subutex®, Temgesic®)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physically dependent, short-acting opioid user</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than 1 hour ago</td>
<td>Precipitated withdrawal</td>
<td>Precipitated withdrawal</td>
<td>Precipitated withdrawal</td>
</tr>
<tr>
<td>More than 12 hours ago</td>
<td>Agonist effect</td>
<td>Attenuated agonist effect</td>
<td>Agonist effect</td>
</tr>
<tr>
<td>Physically non-dependent short-acting opioid user</td>
<td>Agonist effect</td>
<td>Attenuated agonist effect**</td>
<td>Agonist effect</td>
</tr>
<tr>
<td>Buprenorphine maintenance (BMT)*</td>
<td>Agonist effect</td>
<td>Attenuated agonist effect**</td>
<td>Agonist effect</td>
</tr>
<tr>
<td>Methadone maintenance (MMT)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12–24 hours ago</td>
<td>Precipitated withdrawal</td>
<td>Precipitated withdrawal</td>
<td>Precipitated withdrawal</td>
</tr>
<tr>
<td>24–48 hours ago</td>
<td>Precipitated withdrawal if high dose MMT or possible agonist effect if low dose MMT</td>
<td>Precipitated withdrawal due to intravenous naloxone</td>
<td></td>
</tr>
</tbody>
</table>

Notes

* BMT includes buprenorphine preparations with or without naloxone.

** Attenuated agonist: agonist effects will occur only after the naloxone has left the receptor allowing the buprenorphine to become unopposed and resulting in a delayed effect (ie, no initial rush).
As is evident from the above table, the people most likely to misuse buprenorphine (with or without naloxone) are those for whom the effect of using will be favourable (ie, people who are not physically dependent on opioids, people who have used opioid agonists such as morphine more than 12 hours ago and people on buprenorphine maintenance).

Injecting diverted sublingual buprenorphine, can result in fungal endophthalmitis (Aboltins et al 2005) and complications related to injecting tablet formulations such as vein damage, abscesses, infections, and blood borne virus transmission (Jenkinson et al 2005).
Pharmacology

Opioid receptors

Opioid receptors are found throughout the brain and spinal cord, in the gastrointestinal system, parts of the autonomic nervous system, and on white cells. Thus opioid drugs have diverse actions on many organ systems but the most prominent effects are exerted on the central nervous system and the gastrointestinal tract.

Clinically the three most important subtypes of opioid receptor are:
- mu (µ)
- kappa (κ)
- delta (δ).

Mu and delta receptors are involved in systems that influence mood, reinforcing behaviours, respiration, pain, blood pressure and endocrine and gastrointestinal function. Kappa receptors, when activated, can produce endocrine changes and analgesia, but appear to produce dysphoria rather than euphoria (Jaffe 1992).

Full, partial and antagonist properties of the mu opioid receptor

Opioids with an affinity for the mu receptor are classified into three groups.
- full agonist opioids
- partial agonist opioids
- antagonist opioids.

Their effects are shown diagrammatically in Figure 1.

Full agonist opioids

Full agonist opioids are drugs that bind to and activate the opioid receptor. They have a high intrinsic activity at the mu receptor and include heroin, morphine and methadone. Any increase in dose will produce an increase in effect up to a maximum level that is likely to be over the lethal dose range, thereby causing respiratory depression and overdose.

Partial agonist opioids

Partial agonist opioids are drugs that bind to and activate the opioid receptor. They have a lesser amount of intrinsic activity at the mu receptor than full agonist drugs and produce a maximum level of effect lower than that of full agonists. This effect is likely to be under the lethal dose range, and is also known as a ‘ceiling effect’. Buprenorphine is one such drug.
Antagonists

Antagonists are drugs that bind to but do not activate the receptor. They have no intrinsic activity at the mu receptor but can block the site so that no agonist (partial or full) can produce an effect (eg, naltrexone and naloxone).

Figure 1: Effect of three types of opioid with an affinity for the mu receptor

Pharmacology of buprenorphine alone

Buprenorphine is a semi-synthetic opioid derived from the morphine alkaloid, thebaine. It acts as a partial agonist (lesser known as an agonist-antagonist), exerting partial agonist effects at the mu receptor and antagonist effects at the kappa receptor (Johnson et al 2003b; Reckitt Benckiser 2005).

Buprenorphine has low intrinsic activity but a high affinity for the mu opioid receptor, meaning that it binds tightly but does not ‘turn on’ the receptor fully. Buprenorphine also has high affinity for the kappa opioid receptor but no intrinsic activity (Johnson et al 2003b). This results in a milder, less euphoric, and less sedating effect compared with full agonists like heroin and morphine (Lintzeris et al 2001a), which usually provides a sufficient opioid effect to diminish or prevent cravings and opioid withdrawal in opioid-dependent people.

Although buprenorphine has a short half-life its high receptor affinity means that it dissociates slowly from the mu receptor. This results in a long duration of action (Raisch et al 2002), resulting in minimal blood level fluctuations, and prevents opioid withdrawal symptoms when taken regularly.

When buprenorphine is given at higher doses, subsequent illicit opioid doses are blockaded, because of the slow dissociation from the mu receptor.

Buprenorphine has a ceiling dose effect whereby increased doses after a certain point produce no further opioid effects, but extend the duration of action. Investigations into less-than-daily dosing of buprenorphine have been carried out, because of its long duration of action and slow onset of withdrawal symptoms. Buprenorphine alone or in combination with naloxone is effective in less-than-daily dispensing regimens (Johnson et al 2003b; Petry et al 2001).
Less-than-daily dispensing regimens could make buprenorphine more acceptable to clinicians as clients need fewer clinic visits and can take smaller quantities home (Walsh and Eissenberg 2003). Less-than-daily dosing reduces the time pharmacists need to spend supervising clients and may reduce the quantity of medication able to be diverted to the black market. A benefit for clients is that they do not have to attend the pharmacy each day.

In summary, buprenorphine compared with methadone has:
- less intrinsic activity (ie, it produces a smaller opioid effect)
- higher opioid receptor affinity (ie, it will attach to the receptor in preference to other opioids)
- ceiling effects at higher doses (ie, it is safer in overdose)
- a slower dissociation from the opioid receptor (ie, it has milder withdrawal symptoms, so less-than-daily dosing regimens are possible).

Pharmacology of naloxone alone
Naloxone is an antagonist at the kappa, mu and sigma opioid receptors (Strain et al 1997) and has no opioid agonist activity (Raisch et al 2002). It has estimated potency differences between the parental and sublingual routes of 1 : 10–20 (Preston et al 1990).

Pharmacology of buprenorphine in combination with naloxone (Suboxone®)
Suboxone® uses the different sublingual bioavailabilities of buprenorphine and naloxone, so that when it is administered sublingually the buprenorphine has the dominant effect. If the Suboxone® dose is injected, naloxone (which has a low sublingual bioavailability but a high intravenous bioavailability) will dominate, causing opioid withdrawal signs and symptoms (Ling 2001).

Pharmacokinetics of buprenorphine alone
Buprenorphine has a very poor oral bioavailability. A sublingual tablet has been formulated which escapes first-pass metabolism and results in therapeutic levels in the blood stream. It takes about 2–10 minutes for the tablet to dissolve when used sublingually.

Plasma concentrations peak about 60–90 minutes after buprenorphine has been administered, with the clinical effect peaking after 1–4 hours. As the dose increases the opioid effects plateau (ie, the ceiling effect) and the duration of action lengthens. This increase in duration of action allows less-than-daily dosing. The ceiling effect results in a less than maximal opioid effect being produced compared to that produced by full agonists, but it increases buprenorphine’s safety profile.
A rapid distribution phase occurs with buprenorphine’s distribution half-life being 2–5 hours (Reckitt Benckiser 2005). Thus, buprenorphine is highly lipophilic and will penetrate the blood–brain barrier rapidly (Reckitt Benckiser 2005). It is 96 percent protein bound (Johnson et al 2003b; Reckitt Benckiser 2005).

Buprenorphine is metabolised in the liver and small intestine. Metabolism is through glucuronide conjugation and N-dealkylation through the cytochrome P4503A4 (CYP4503A4) route to norbuprenorphine (the major metabolite) (Reckitt Benckiser 2005). Buprenorphine and its metabolites go through enterohepatic recycling, which leads to the drug’s slow excretion. Norbuprenorphine (a weak mu agonist) is considered to be inactive (Reckitt Benckiser 2005).

Buprenorphine is a weak competitive inhibitor of CYP4503A4 and 2D6 isoenzymes (Reckitt Benckiser 2005), which are important enzyme pathways for drug interactions.

The elimination half-life of buprenorphine is around 34.6 hours (20.4–72.9 hours) (Reckitt Benckiser 2005). Excretion occurs mainly via the biliary route with around 70 percent excreted through the faeces and the remainder through the urine (Reckitt Benckiser 2005).

This information is summarised in Table 3.

Table 3: Summary of pharmacokinetics of buprenorphine alone

<table>
<thead>
<tr>
<th>Effect</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sublingual dissolution time</td>
<td>2–10 minutes</td>
</tr>
<tr>
<td>Peak plasma concentration</td>
<td>60–90 minutes</td>
</tr>
<tr>
<td>Onset of clinical effects</td>
<td>30–60 minutes</td>
</tr>
<tr>
<td>Peak clinical effects</td>
<td>1–4 hours</td>
</tr>
<tr>
<td>Duration of effects</td>
<td>8–12 hours at low dose (eg, 2 mg)</td>
</tr>
<tr>
<td></td>
<td>24–72 hours at high dose (eg, &gt;16 mg)</td>
</tr>
<tr>
<td>Distribution half-life</td>
<td>2–5 hours</td>
</tr>
<tr>
<td>Elimination half-life</td>
<td>34.6 hours</td>
</tr>
<tr>
<td>Precipitated withdrawal effects</td>
<td></td>
</tr>
<tr>
<td>• Begin</td>
<td>30–90 minutes</td>
</tr>
<tr>
<td>• Peak</td>
<td>1–4 hours</td>
</tr>
<tr>
<td>• Duration</td>
<td>Up to 12 hours</td>
</tr>
</tbody>
</table>

Pharmacokinetics of naloxone alone

Naloxone given sublingually has a poor absorption rate as less than 10 percent becomes bioavailable (Bell et al 2004). It is most effective when given parentally when the effects are seen within 1–2 minutes of an intravenous dose.

Naloxone is highly lipid soluble. After intravenous administration the distribution half-life is around 4 minutes.
Naloxone crosses the placenta easily, but its excretion in breast milk is unknown.

Naloxone is about 45 percent bound to plasma proteins. Its plasma half-life is one hour (Bell et al 2004).

Naloxone undergoes extensive metabolism with almost none of the drug being excreted unchanged. It is metabolised primarily to naloxone-3-glucuronide (inactive) and to a lesser extent 6-B-naloxol (active).

Naloxone is eliminated largely through the urine, with an elimination half-life of 60–90 minutes.

Naloxone tastes bitter.

**Pharmacokinetics of buprenorphine with naloxone**

The bioavailability of buprenorphine-alone tablets appear to be slightly less than the combination tablet. The combination tablet provides higher trough concentrations of norbuprenorphine (Strain et al 2004). However, when buprenorphine-alone tablets or buprenorphine with naloxone tablets are taken sublingually, the products have indistinguishable actions from each other (Bell et al 2004).

The sublingual absorption of buprenorphine with naloxone can vary widely among patients (Reckitt Benckiser 2005).

**Contraindications and precautions for buprenorphine (with or without naloxone)**

Contraindications for buprenorphine (with or without naloxone) include (Reckitt Benckiser 2005):

- hypersensitivity to buprenorphine or naloxone or any other component of the tablet
- children aged under 16
- severe respiratory or hepatic insufficiency (Child-Pugh B or C disease)
- acute intoxication with alcohol or other CNS depressants
- pregnant women
- breast-feeding women.

Precautions for buprenorphine (with or without naloxone) include (Reckitt Benckiser 2005):

- dysfunction of the biliary tract
- hypotension, prostatic hypertrophy and urethral stenosis
- compromised respiratory function (eg, chronic obstructive pulmonary disease, cor pulmonale, decreased respiratory reserve, hypoxia, hypercapnia or pre-existing respiratory depression)
concomitant administration of buprenorphine with central nervous system (CNS) depressants such as opioids, sedatives, general anaesthetics, alcohol and phenothiazines

- hepatitis and hepatic events (hepatic necrosis and hepatitis with jaundice have been reported with buprenorphine use)

- pre-existing or acquired mitochondrial impairment (genetic diseases, viral infections particularly chronic hepatitis C, alcohol abuse, anorexia) and associated mitochondrial toxins (eg, aspirin, isoniazid, valproate, amiodarone, antiviral nucleoside analogues) which could promote the occurrence of hepatic injuries

- head injury or increased cerebrospinal pressure.

Care should also be taken if the person:

- has impaired renal function

- has adrenal cortical insufficiency (eg, Addison’s disease)

- is showing CNS depression

- is elderly

- is debilitated.

**Common side effects and adverse effects**

The most common adverse events for buprenorphine (with or without naloxone) are those related to withdrawal symptoms (eg, abdominal pain, diarrhoea, muscle aches, anxiety and sweating). In patients with marked drug dependence, initial administration of buprenorphine can produce a withdrawal effect similar to that associated with naloxone (Reckitt Benckiser 2005).

Most adverse effects experienced by patients occur early in treatment, are mild and subside with time. They appear to be generally unrelated to buprenorphine dose, however nausea is more common with doses over eight milligrams, and dizziness occurs more commonly at high doses (Lintzeris 2006).

The management of opioid related side effects should be the same as that for other opioid pharmacotherapies.

Tables 4 and 5 summarise the adverse effects for buprenorphine (with or without naloxone).
Table 4: Very common adverse events reported by at least 10 percent of subjects

<table>
<thead>
<tr>
<th>Part of the body affected</th>
<th>Very common adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body as a whole</td>
<td>Headache,* withdrawal syndrome</td>
</tr>
<tr>
<td>Digestive system</td>
<td>Constipation, nausea</td>
</tr>
<tr>
<td>Nervous system</td>
<td>Insomnia</td>
</tr>
<tr>
<td>Skin and appendages</td>
<td>Sweating</td>
</tr>
</tbody>
</table>

Note
* Headache occurs during induction, because of the high uptake of buprenorphine on to the opioid receptors.


Table 5: Common adverse events reported by at least 1 percent of subjects

<table>
<thead>
<tr>
<th>Part of the body affected</th>
<th>Common adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body as a whole</td>
<td>Asthenia, chills, fever, flu syndrome, infection, malaise, abdominal pain, back pain, chest pain, pain, accidental injury</td>
</tr>
<tr>
<td>Cardiovascular system</td>
<td>Migraine, hypertension, vasodilation</td>
</tr>
<tr>
<td>Digestive system</td>
<td>Anorexia, diarrhoea, nausea/vomiting, dyspepsia, liver function abnormal, flatulence</td>
</tr>
<tr>
<td>Metabolic/nutritional disorders</td>
<td>Peripheral oedema, weight decreased</td>
</tr>
<tr>
<td>Musculoskeletal system</td>
<td>Arthralgia, leg cramps, myalgia</td>
</tr>
<tr>
<td>Nervous system</td>
<td>Anxiety, depression, dizziness, hypertonia, nervousness, paresthesia, somnolence, thinking abnormal, libido decreased</td>
</tr>
<tr>
<td>Respiratory system</td>
<td>Cough increased, pharyngitis, rhinitis</td>
</tr>
<tr>
<td>Skin and appendages</td>
<td>Rash, pruritus, urticaria</td>
</tr>
<tr>
<td>Special senses</td>
<td>Lacrimation disorder, amblyopia</td>
</tr>
<tr>
<td>Urogenital system</td>
<td>Impotence, urine abnormality</td>
</tr>
</tbody>
</table>


Cases of acute and chronic hypersensitivity to buprenorphine have been reported in clinical trials and in the post-marketing experience. The most common signs and symptoms include rashes, hives and pruritus. Cases of bronchospasm, angioneurotic oedema and anaphylactic shock have been reported (Reckitt Benckiser 2005).

Other side effects include tooth decay due to lowered saliva production and changes to menstrual cycles (either a return to normal after illicit drug use or continued irregularities) (Lintzeris et al 2001a).

Drug interactions

Pharmacodynamic drug interactions
Other drugs with activity at opioid receptors (ie, opioid agonists and antagonists) interact with buprenorphine.
Drugs such as benzodiazepines with the potential to cause central nervous system depression may cause additive sedative and respiratory depressant effects when taken with buprenorphine.

**Pharmacokinetic drug interactions**

If buprenorphine is taken in conjunction with drugs which either induce (increase the activity of) or inhibit (decrease the activity of) the cytochrome P450 isoenzyme 3A4, clinically significant drug interactions may occur.

In particular, care should be taken when CYP4503A4 inhibitors (eg, protease inhibitors, ketoconazole, nifedipine, erythromycin and clarithromycin) are prescribed in combination with buprenorphine as these may cause an increase in blood plasma levels of buprenorphine.

See Appendix A for drug interactions with buprenorphine (with or without naloxone).
General Information

Formulation of Subutex® and Suboxone®
Subutex® contains buprenorphine hydrochloride alone. It is a white biconvex tablet and comes in two dosages: 2 mg and 8 mg.

Buprenorphine hydrochloride alone is unavailable in New Zealand.

Suboxone® contains buprenorphine hydrochloride and naloxone. It is a white, hexagonal tablet that is taken sublingually. It contains:
- 2 mg of buprenorphine and 0.5 mg of naloxone
- 8 mg of buprenorphine and 2 mg naloxone.

Suboxone® is lemon-lime flavoured.

Controlled drug classification of Suboxone®
Suboxone® is a controlled drug, class C4. This means that there is no requirement to use a controlled drug form to prescribe this medication. Prescriptions should be written standard prescription forms.
Induction on to Buprenorphine (with or without Naloxone)

Pharmacotherapy selection

For maintenance treatment buprenorphine and methadone have comparable treatment outcomes. The client and the prescriber should decide together the best treatment option.

Buprenorphine (with or without naloxone) should be given as an opioid-dependence treatment option only after the client’s dependence has been ascertained:

- through documented regular opioid use
- according to DSM-IV criteria (APA 1994)
- with a positive opioid urinalysis.

The following information has been adapted from the *Australian National Clinical Guidelines and Procedures for the Use of Buprenorphine in the Treatment of Opioid Dependence* (Lintzeris et al 2006).

Key treatment outcomes for maintenance buprenorphine and methadone treatments are comparable, and the differences between these treatments are small compared to the variability in outcomes between patients and between programs. Flexible, high dose methadone maintenance appears to have a slightly greater efficacy than flexible dose buprenorphine maintenance with respect to client retention. Clients and clinicians may develop a preference, depending on:

- the client’s response to treatment
- individual variations in absorption, metabolism and clearance rates
- adverse events
- the flexibility of dosing
- client and clinician expectations.

Consider buprenorphine (with or without naloxone) for any opioid-dependent client, especially if they:

- are young
- have a brief history of opioid dependence
- smoke opioids or take them orally
- have young children
- have side effects from methadone
- have failed to benefit from methadone previously
- would prefer not to take methadone.
Clients with a high tolerance to opioid effects (ie, using doses of morphine or methadone greater than the equivalent of 40 to 60mg of methadone) can be successfully inducted onto maintenance treatment with buprenorphine (with or without naloxone). Research indicates that although this induction may be more difficult and complex it can still be successful.

Methadone used to be thought the most suitable opioid-substitution treatment for clients who were misusing benzodiazepines. However, these clients can be prescribed buprenorphine, as it is no less safe than co-administered methadone and benzodiazepines and may, in fact, prove to be safer. Research is being undertaken in this area.

Some clients must not be prescribed buprenorphine (with or without naloxone). See ‘Contraindications and precautions for buprenorphine (with or without naloxone)’, page 13.

**Induction**

Induction on to buprenorphine (with or without naloxone) involves a very different philosophy to that of induction on to methadone. Methadone induction aims to ‘start low and go slow’. Buprenorphine induction should reflect the need to avoid causing precipitated withdrawal when giving the first few doses. Once this is achieved then the dose may safely be rapidly titrated up to an effective level to prevent clients dropping out of treatment.

**Response to treatment**

Individuals may experience considerable pharmacokinetic and pharmacodynamic differences in their response to different opioid-substitution pharmacotherapies.

A medication’s continued use depends on its ability to meet the treatment goals. This means the treatment team and the client should identify the client’s treatment goals and decide how those goals are to be assessed.

When the agreed goals are not being met, the treatment should be reviewed, including the role of psychosocial interventions, the levels of monitoring and supervision, the dose of the substitution opioid, and alternate pharmacotherapies. For example, clients who cannot stabilise their continued used of illicit opioids, even on high doses of buprenorphine, may be better suited to higher doses of a full agonist such as methadone.

**Adverse events**

Individuals experiencing significant side effects from one opioid medication may benefit from treatment with an alternative medication. Individuals complaining of continued sedation under methadone may prefer buprenorphine.
Flexibility of dosing
Once a client is stabilised on a daily dosing regime of buprenorphine, they may be able to switch to a less-than-daily dosing regimen. This may be more convenient for clients and reduce the need for takeaways (thus, minimising the risk of misuse or diversion). However, not all clients are comfortable with less-than-daily dosing and may require or prefer daily dosing.

Withdrawal from substitution treatment
As buprenorphine is only a partial agonist and dissociates slowly from the opioid receptors, it has a milder withdrawal syndrome than methadone. However, rates of relapse to illicit use are comparable for both methadone and buprenorphine.

Client and clinician expectations
The introduction of new pharmacotherapies can result in clients, clients' families and service providers having unrealistically positive expectations about the possible outcomes. This can affect the treatment’s perceived outcomes.

Capacity for transfer from methadone substitution
Some clients require high doses of methadone to stabilise their opioid use, so a marked reduction in their methadone dose may cause them to relapse to regular opioid use. These clients may not benefit from buprenorphine, as it may be difficult for them to transfer from high methadone doses and/or stabilise on buprenorphine treatment.

Conversely, these clients may benefit from buprenorphine’s greater mu receptor affinity.

Precipitated withdrawal
Precipitated withdrawal occurs because buprenorphine has a higher affinity for the opioid receptor than full agonists such as morphine or methadone, which causes these drugs to be knocked off the opioid receptor site. This causes a net reduction in the total opioid effect because buprenorphine is only a partial agonist at the receptor site, resulting in clients experiencing opioid-withdrawal symptoms.

Opioid withdrawal and precipitated withdrawal occur at different times. Precipitated withdrawal occurs when buprenorphine has been given recently and is attaching to the opioid receptors and displacing other opioids (ie, during the distribution phase). Opioid withdrawal tends to occur when the dose of an opioid taken earlier starts to wear off. Buprenorphine-precipitated withdrawal usually begins within 30–90 minutes of administration, peaking 1–4 hours after the first buprenorphine dose.

Withdrawal symptoms are mild to moderate in severity and can last up to 12 hours (see Figure 2).
Figure 2: Severity of withdrawal over time

![Chart showing severity of opioid withdrawal over time.](chart)

Note: BUP = buprenorphine.

If precipitated withdrawal symptoms occur, it is important the client does not use other opioids to relieve the symptoms, because this will prolong the stabilisation process and may result in the client dropping out of treatment. Advise the client to return for assessment and prescribe symptomatic medication if needed.

Subsequent doses of buprenorphine (with or without naloxone) are less likely to precipitate withdrawal symptoms.

Rapid titration of the dose over the first few days will decrease the risk of client drop-out from treatment. Client retention is increased if they are informed about precipitated withdrawal and what to do if it occurs. Increasing the time interval between the last opioid dose used and the first dose of buprenorphine (with or without naloxone) reduces the risk of precipitated withdrawal.

**Transfer from street drugs (illicit opioid use)**

**Induction and stabilisation**

In this section, medication doses (eg, 8 mg of buprenorphine) refer to the buprenorphine dose regardless of whether naloxone is present.

As buprenorphine is a partial agonist at the opioid receptor, induction regimens can be more rapid than those with full agonists such as methadone.

Serious adverse effects such as overdose or treatment drop-out are more likely to occur if the client self-medicates their withdrawal symptoms with drugs such as opioids, alcohol and benzodiazepines.
**Rules of induction**

- Rapid titration is the key to a successful induction. Prescribers should aim to achieve a dose of 12 to 16 mg by day three (Lintzeris et al 2006).
- The most important factor in preventing precipitated withdrawal is not the timeframe but whether the client is showing opioid withdrawal signs. Wait until objective signs of opioid-withdrawal are present before giving the first dose of buprenorphine.
- Splitting the first daily dose into a twice-daily dose reduces the chance of precipitated withdrawal.
- Giving the first dose early in the day allows the ability to manage precipitated withdrawal if it occurs.

**Equivalences**

- Four milligrams of buprenorphine is at least equivalent to 40–60 mg of intravenous morphine.
- Sixteen milligrams of buprenorphine is at least equivalent to 100–120 mg of intravenous morphine (Johnson et al 2003b).

**Timing of first dose**

As a general guide, the first dose of buprenorphine (with or without naloxone) should be administered at least:

- 12 hours after the last dose of intravenous morphine or home-bake
- 12–24 hours after an oral use of morphine or poppy-seed tea
- 24–48 hours after the last dose of oral or intravenous methadone.

It is difficult to ascertain approximate timeframes for poppy-seed tea withdrawal, as it depends on how much and how often it was used in a 24-hour period. Unlike morphine or methadone, poppy-seed tea may be sipped slowly throughout the day.

Administering the first dose within the above timeframes may precipitate withdrawal as buprenorphine displaces other drugs from the receptor.

**Advice to clients**

Advise clients to cease their use of illicit opioids and all opioid-based medications including codeine-based products, as these medications increase the difficulty of the transfer process.

**Precipitated withdrawal**

Prescribe symptomatic withdrawal medication if needed. See ‘Precipitated withdrawal’, page 20, for more information.
Review of dose

The prescribing doctor or another member of the treatment team should review the client regularly; at least daily for the first three days then every two to four days during the induction phase.

The prescriber should be aware of other CNS-depressant medications the client is taking concurrently with buprenorphine.

Titration of dose

The dose should be titrated according to the client’s:

- reported intoxication, withdrawal and craving over the preceding 24 hours
- additional drug use and reason for this use stated by the client
- experience of side effects or other adverse effects
- adherence to the dosing regimen
- satisfaction with the buprenorphine dose.

The schedules in Tables 6 and 7 give examples of induction regimens.

Table 6: Schedule 1: Buprenorphine (with or without naloxone) doses for the first three days of treatment

<table>
<thead>
<tr>
<th>Day</th>
<th>Buprenorphine (with or without naloxone) dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2–4 mg plus 0–4 mg</td>
</tr>
<tr>
<td>2</td>
<td>4–12 mg</td>
</tr>
<tr>
<td>3</td>
<td>6–16 mg</td>
</tr>
</tbody>
</table>

For clients who present using high doses of opioids more rapid titration of the dose can occur. This reduces the likelihood of client drop-out and illicit use during the induction process. Table 7 gives an example of a more rapid induction regime.

Table 7: Schedule 2: Buprenorphine (with or without naloxone) doses for the first three days of treatment

<table>
<thead>
<tr>
<th>Day</th>
<th>Buprenorphine (with or without naloxone) dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4 mg plus 0–8 mg</td>
</tr>
<tr>
<td>2</td>
<td>12–20 mg</td>
</tr>
<tr>
<td>3</td>
<td>20–24 mg</td>
</tr>
</tbody>
</table>

Effect of ongoing illicit opioid use

After the first dose of buprenorphine, subsequent doses should be associated with only light or minimal withdrawal discomfort, if the client has not used illicit opioids during the intervening period.
Clients who continue to use illicit opioids between their first and second doses of buprenorphine may have difficulty stabilising on the treatment and experience ongoing symptoms of opioid withdrawal (Lintzeris et al 2001a).

**Stabilisation**

Within less than one week of commencing treatment, clients should achieve maintenance on buprenorphine (with or without naloxone).

**Summary of procedure for transferring a client from illicit drugs**

The following summary has been adapted from the Australian National Clinical Guidelines and Procedures for the Use of Buprenorphine in the Treatment of Heroin Dependence (Lintzeris et al 2001a).

Table 8 summarises the procedure for transferring a client from illicit drugs.

**Table 8:** Summary of procedure for prescribers transferring a client from illicit drugs

<table>
<thead>
<tr>
<th>Step</th>
<th>Action</th>
</tr>
</thead>
</table>
| 1    | Prepare the client for the transition by:  
  - telling them to clear significant work or other commitments from their calendar  
  - giving them information about the treatment and what will happen  
  - organising support for them  
  - communicating with the pharmacist and other staff. |
| 2    | Tell the client to stop using illicit, prescribed or over-the-counter opioids, because you cannot administer buprenorphine (with or without naloxone) until you observe the client showing significant opioid-withdrawal symptoms. Ask the client how many hours it is before they usually begin to feel uncomfortable after their last opioid dose. This is usually:  
  - 12 hours after the last dose of intravenous morphine or home-bake  
  - 12–24 hours after an oral dose of morphine or poppy-seed tea  
  - 24–48 hours after the last dose of oral or intravenous methadone. |
| 3    | On Day 1 administer the first dose of 2–8 mg of buprenorphine (with or without naloxone). |
| 4    | Review the client 1–4 hours after the first dose of buprenorphine (with or without naloxone) and assess the client for precipitated withdrawal.  
  **If client's precipitated withdrawal is ...**  
  **then ...**  
  - worsening  
    - For the remainder of the day, provide:  
      - symptomatic medication  
      - no further doses.  
  - not worsening or improving  
    - After at least four hours, administer a further 2–8 mg of buprenorphine (with or without naloxone). |
| 5    | On Day 2, review the client before giving them another dose of buprenorphine (with or without naloxone). If the client has responded well to the first dose/s, increase the dose to 6–20 mg. |
Review the client frequently. Increase the dose of buprenorphine (with or without naloxone) until stabilisation is achieved. Note: Doses of 16–24 mg can be reached within three days.

Transfer from methadone substitution treatment

Transferring previously stable clients from methadone to buprenorphine carries a risk of destabilisation for the client. Appropriate monitoring and support should be provided and transfers should be planned. If destabilisation occurs a return to methadone maintenance may be the best option (Lintzeris 2006).

Transfer from 40 mg or less of methadone

When methadone clients take a dose of buprenorphine, the buprenorphine displaces methadone from the mu opioid receptors. This causes a net reduction in opioid activity, because buprenorphine has less intrinsic action at the receptors than methadone.

Clients on low doses of methadone (eg, less than 30 mg) generally tolerate this transition with minimal discomfort, but it can still cause a precipitated withdrawal.

Minimise the chance of precipitated withdrawal

To minimise the chance of precipitated withdrawal, clients should be on a methadone dose of less than 40 mg (ideally 30 mg or less) for at least one week before starting buprenorphine (Reckitt Benckiser 2005).

Clients should stop using methadone and all opioid-based medications including codeine-based products before starting buprenorphine, because these medications increase the difficulty of transferring.

An approach of repeated small doses for the first day of induction minimises the risk of causing precipitated withdrawal (ie three times daily dosing as opposed to twice daily dosing) (Lintzeris et al 2006).

Administer the first dose of buprenorphine (with or without naloxone) only when the client experiences mild to moderate observable opioid withdrawal signs. Usually this is at least 24 hours after the last methadone dose.

The risk of a precipitated withdrawal may be further reduced by ensuring the last dose of methadone is taken in the morning and the first dose of buprenorphine (with or without naloxone) is taken late the following day (Lintzeris et al 2001a). This can be done in an inpatient setting with monitoring available 24 hours a day. In an outpatient setting, it is best to give the first dose in the morning, so monitoring and support can occur during clinic hours.

Precipitated withdrawal symptoms

Prescribe symptomatic withdrawal medication if needed (eg, clonidine).
See ‘Precipitated withdrawal’, page 20, and Appendix B: ‘Medications to relieve the symptoms of opioid withdrawal’ for more information.

**Conversion rates**

Use the conversion rates in Table 9 for low-dose methadone transfer.

**Table 9: Conversion rates for low-dose methadone transfer**

<table>
<thead>
<tr>
<th>Last oral methadone dose</th>
<th>Initial buprenorphine (with or without naloxone) dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 mg or greater</td>
<td>2 mg plus 0–4 mg plus 0–4 mg</td>
</tr>
<tr>
<td>less than 30 mg</td>
<td>4 mg plus 0–4 mg plus 0–4 mg</td>
</tr>
</tbody>
</table>

Source: Lintzeris et al 2006

See Table 10 for a summary of the procedure for transferring a client from methadone to buprenorphine.

**Begin rapid titration**

On day 2, if the client has experienced no precipitated withdrawal, begin rapid titration.

**Transfer from more than 40 mg of methadone**

**Methadone doses of 40–60 mg**

Clients can be transferred if they are unable to reduce their methadone dose without destabilising. It is possible to transfer from methadone doses of 40–60 mg, but inform the client of the difficulty of transferring from this level and that it increases the chance of precipitated withdrawal and of the client feeling more uncomfortable during the transfer period (Chadderton 2000).

**Methadone doses of more than 60 mg**

Clients unable to reduce to 60 mg of methadone should generally not attempt to transfer to buprenorphine as outpatients (Lintzeris et al 2001a).

**Option 1: Use of inpatient unit and/or reduction in methadone dose**

Admit the client to an inpatient unit and/or reduce the client’s methadone dose from 60 mg to 30 mg over a period of up to three days to reduce the client’s physical dependence. This does not significantly increase withdrawal discomfort (Greenwald et al 2003).

Prescribe symptomatic withdrawal medication, including clonidine, to ease the discomfort of the transfer. See Appendix B for more information.

Advise the client to stop taking all opioid-based medications, including codeine-based products, as these increase the difficulty of the transfer process.
Cease methadone dosing. Wait until the client experiences mild to moderate symptoms and observable opioid-withdrawal signs, then administer the first buprenorphine dose. Usually when transferring clients from higher methadone doses this occurs 48–96 hours after the last methadone dose.

**Option 2: Short-term transfer to morphine**
Transfer the client to morphine for three to four days, then transfer them to buprenorphine (with or without naloxone).

**Precipitated withdrawal**
Symptomatic medication will probably be needed with high-dose transfer to ease the discomfort of the induction process.

See ‘Precipitated withdrawals’, page 20, and Appendix B: ‘Medications to relieve the symptoms of opioid withdrawal’ for more information.

**Equivalences**
Sixteen milligrams of buprenorphine daily is at least equivalent to 60 mg of methadone.

Eight milligrams of buprenorphine daily is at least equivalent to 40 mg of methadone (Johnson et al 2003b).

These equivalences are approximate and vary markedly between individuals.

**Summary of transfer from methadone substitution treatment**
The following summary has been adapted from the *Australian National Clinical Guidelines and Procedures for the Use of Buprenorphine in the Treatment of Heroin Dependence* (Lintzeris et al 2001a) and *National Clinical Guidelines and Procedures for the Use of Buprenorphine in the Treatment of Opioid Dependence* (Lintzeris et al 2006).

Table 10 summarises the procedure for transferring a client from methadone substitution treatment.
Table 10: Summary of procedure for transferring a client from methadone substitution treatment

<table>
<thead>
<tr>
<th>Step</th>
<th>Action</th>
</tr>
</thead>
</table>
| 1 | Prepare the client for the transition by:  
• telling them to clear significant work or other commitments from their calendar  
• giving them information about the treatment and what will happen  
• organising support for them  
• communicating with the pharmacist and other staff. |
| 2 | Tell the client to stop using methadone and do not dispense buprenorphine (with or without naloxone) until you observe the client showing significant opioid-withdrawal symptoms. Ask the client how many hours it is before they usually begin to feel uncomfortable after their last methadone dose (usually 48–96 hours). Prescribe symptomatic medications in limited amounts in the intervening period if necessary. |
| 3 | On Day 1 administer the first dose of 2–4 mg of buprenorphine (with or without naloxone). |
| 4 | Review the client one hour after the first dose of buprenorphine (with or without naloxone) and assess them for precipitated withdrawal.  

<table>
<thead>
<tr>
<th>If client's precipitated withdrawal is ...</th>
<th>then ...</th>
</tr>
</thead>
</table>
| worsening | For the remainder of the day, provide  
• symptomatic medication  
• no further doses. |
| improving | After four hours a further 2–4 mg dose can be given and this may be repeated another four hours later. |
| neither improving nor worsening (ie, not developing precipitated withdrawal but not gaining any relief from the buprenorphine (with or without naloxone) already administered. | Administer a second dose of 2–4 mg and observe the client for another hour. If the client’s symptoms improve a further 2–4 mg can be administered in another four hours. |
| 5 | On Day 2, review the client before giving them another dose of buprenorphine (with or without naloxone). If the client has responded well to the first dose, they can usually tolerate an increased dose of 8 mg. |
| 6 | Review the client frequently. Increase the dose of buprenorphine (with or without naloxone) until stabilisation is achieved. Note: Doses of around 16 mg can be reached within two to three days. |
Buprenorphine (with or without Naloxone) Substitution

Stabilisation period

Daily dosing is recommended during the stabilisation period. Monitor clients regularly.

It takes three to seven days for new steady-state blood levels to be reached after the last dose change. After the induction period, adjust the dose at three- to seven-day intervals. Increases are summarised in Table 11.

<table>
<thead>
<tr>
<th>Buprenorphine (with or without naloxone) dose</th>
<th>Buprenorphine (with or without naloxone) dose increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 16 mg</td>
<td>2–8 mg</td>
</tr>
<tr>
<td>16 mg or more</td>
<td>4–8 mg</td>
</tr>
</tbody>
</table>


As buprenorphine is a partial agonist, increases in dose may not produce the corresponding increase in effects such as euphoria, but they may provide better cross-tolerance to other opioids and reduce ‘use on top’ (Johnson et al 2003b).

The stabilisation period is made more difficult if the client continues to ‘use on top’ of the buprenorphine dose.

Substitution treatment

Generally, effective substitution treatment doses are in the range of 8–24 mg of buprenorphine (with or without naloxone) per day, although some clients with lower dependencies may be comfortable on smaller doses. If clients continue to ‘use on top’, increase the dose of buprenorphine.

With time, the maintenance dose can be reduced without a loss of clinical effectiveness (Ling and Smith 2002).

There is evidence to suggest that daily doses of 4 mg or less of buprenorphine will result in client outcomes similar or worse than those which would be expected with 20 mg of methadone daily. A dose of 4 mg or less per day of buprenorphine will be less effective at retaining clients in treatment or reducing illicit opioid use than doses greater than 4 mg (Lintzeris et al 2006).

The manufacturer’s recommended maximum daily dose of buprenorphine (with or without naloxone) dose is 32 mg. Some clients have had success with higher doses, but substitution treatment doses higher than 32 mg have not been adequately studied.
Doctors should be aware of the medico-legal implications of prescribing outside licensing provisions.

Higher doses of buprenorphine produce more effective antagonist effects, which block the effect of additional opioid use. However, if clients regularly continue to use on top of their daily buprenorphine (with or without naloxone) doses, buprenorphine may not be the most effective treatment regimen for them. The partial agonist effect may not be ‘strong’ enough, so consider alternative opioid substitution therapy (eg, methadone).

The following summary has been adapted from the Australian National Clinical Guidelines and Procedures for the Use of Buprenorphine in the Treatment of Opioid Dependence (Lintzeris et al 2006).

Transfer from buprenorphine (with or without naloxone) to an alternative pharmacotherapy (eg, methadone) may be indicated if:

- the client has little or no response to an increase in dose of buprenorphine (with or without naloxone)
- the client is already on a high dose of buprenorphine (with or without naloxone)
- an increase in dose is considered unsafe by the prescriber
- the client is persistently diverting their dose, or
- the client attends irregularly, frequently missing scheduled doses.

When the client is stable in the maintenance phase they are eligible for takeaway doses of buprenorphine, if they meet the same criteria as for takeaway doses of methadone. See Practice Guidelines for Opioid Substitution Treatment in New Zealand (Ministry of Health 2008) for guidelines around clients receiving takeaway doses of methadone. Alternatively, they can have a less-than-daily dosing regimen, which requires fewer pharmacy visits but no takeaway medication.

Dosing options including reduced-frequency regimens

Studies indicate that many clients stable on buprenorphine can tolerate a reduced-frequency dosing regimen without experiencing opioid intoxication or withdrawal. This is due to the slow dissociation from the opioid receptor, which provides a long duration of action (Ling and Smith 2002).

Outpatient clinics tend to prefer reduced-frequency dosing regimens (Johnson et al 2003b) with twice- and thrice-weekly dosing as efficacious as daily dosing for promoting treatment retention, opioid abstinence and reductions in HIV-risk behaviour (Marsch et al 2005). Clients generally tolerate the transition quite well but some clients may feel uncomfortable in the last 12 hours or so before their next dose. In these cases dose increases can help, otherwise they should return to daily dosing (Chadderton 2000).

Clients have reported mood swings between dosing and non-dosing days (Chadderton 2000) and it is expected that less than half of clients will prefer alternate day supervised dosing to daily supervised dosing (Lintzeris et al 2006).
Reduced-frequency dosing (Marsch et al 2005):
- is safe, effective and preferred by clients
- reduces the need for clients’ daily attendance at the pharmacy
- is cost effective
- eliminates the risk of takeaway medication being diverted
- can be offered as an incentive to clients.

The *Australian National Clinical Guidelines and Procedures for the Use of Buprenorphine in the Treatment of Opioid Dependence* (Lintzeris et al 2006, p 29) states that:

‘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 clients 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.’

Reduced-frequency dosing regimens include alternate-day, four-times-a-week or three-times-a-week regimens.

Other dosage regimens have been trialled including twice-weekly, every fourth day, and every fifth day dosing, but as the number of subsequent non-dosing days increases, the number of clients who can be managed effectively on these regimens decreases. These regimens will be instigated infrequently, if at all.

**Alternate-day or four-times-a-week dosing regime**

These regimens require the client to attend the pharmacy for dosing on alternate days (ie, dose once every 48 hours), or attend four times a week with three x 48-hour doses and one x 24-hour dose each week (eg, attendance on Monday, Tuesday, Thursday, Saturday). The advantage of the four times a week regime is that the client attends on regular days each week, reducing the likelihood of errors both in attendance by the client and in dosing by the pharmacist (Lintzeris et al 2006).

The following information has been adapted from the *Australian National Clinical Guidelines and Procedures for the Use of Buprenorphine in the Treatment of Heroin Dependence* (Lintzeris et al 2001a).

After a satisfactory period of stabilisation, the client’s frequency of dosing may be decreased to alternate-day dosing at twice the individually titrated daily dose. For example, a patient stabilised to receive a daily dose of 8 mg may be given 16 mg on alternate days, with no medication on the intervening days.
Review the client after the first or second 48-hour dose, and titrate the dose according to the client’s response.

- If the client reports features of intoxication from the buprenorphine during its peak effects (within the first 24 hours), then the 48-hour dose should be reduced.
- If the client reports that the dose did not prevent the onset of opioid withdrawal or craving, or reports sleep difficulties over the 48-hour period, then the 48-hour buprenorphine dose should be increased.

**Three-times-a-week regime**

To try a three-times-a-week regime after a two-week trial on alternate-day or four-days-a-week dosing has been shown to be successful.

Review the client in the week after the first 72-hour dose and titrate the dose accordingly.

If the client cannot be stabilised on a three-times-a-week regime then consider returning the client to four-times-a-week dosing.

Table 12 converts the daily dose to less-than-daily doses.

<table>
<thead>
<tr>
<th>Daily dose (every 24 hours) (mg)</th>
<th>Two-day dose (every 48 hours) (mg)</th>
<th>Three-day dose (every 72 hours) (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>8</td>
<td>12</td>
</tr>
<tr>
<td>6</td>
<td>12</td>
<td>18</td>
</tr>
<tr>
<td>8</td>
<td>16</td>
<td>24</td>
</tr>
<tr>
<td>10</td>
<td>20</td>
<td>30</td>
</tr>
<tr>
<td>12</td>
<td>24</td>
<td>32</td>
</tr>
</tbody>
</table>

Some clients may benefit from total doses greater than 32 mg. However, although results have been promising with less-than-daily-dosing schedules, insufficient evidence exists about higher doses. It is unknown what effects, if any, occur from the larger sublingual naloxone doses in the less-than-daily doses.

Clients on lower doses of buprenorphine may find the less-than-daily regime does not provide them with full cover for the entire period and should change back to daily dispensing. Clients on reducing regimes may need to switch to daily dosing as their buprenorphine dose reaches 4 mg or less (Lintzeris et al 2006)

The registered maximum recommended dose of buprenorphine (with or without naloxone) in New Zealand is 32 mg.
Practitioners should be aware of the medico-legal implications of prescribing doses greater than 32 mg. Frequent clinical and hepatic monitoring is recommended under such circumstances (Lintzeris et al 2001a).

**One-off supervised multiple dose**

If a client is not felt to be safe with takeaway doses and is known to be able to tolerate a less-than-daily dispensing regimen, consider giving them a multiple dose for a particular situation or occasion up to a maximum of 32 mg of buprenorphine as an alternative to takeaway doses.

**Missed doses**

A missed dose of buprenorphine (with or without naloxone) will not cause severe adverse effects due to its high affinity and slow receptor dissociation.

**Daily dosing**

A missed dose on daily dispensing should not precipitate any substantial withdrawal symptoms. Clients on low doses, however, may become uncomfortable. The client should return the following day for their usual dose.

**Less-than-daily dosing**

If a client on alternate-day or three-times-a-week dispensing misses a dosing day and attends on the following non-dosing day, calculate how many days medication they need until the next dosing day. For example clients on:

- alternate-day dosing should be dispensed a 24-hour dose (ie, half the usual 48-hour dose)
- three-times-a-week dosing should be dispensed a 24- or 48-hour dose depending on the length of time until their next normal dispensing day.

**Multiple missed doses**

Clients who have not taken their dose of buprenorphine (with or without naloxone) for three consecutive days (ie, 72 hours) cannot be dispensed to and must be referred to the prescriber for an evaluation of their opioid tolerance, other opioid use and risk of precipitated withdrawal before receiving any further doses.

Some clients find that their less-than-daily dose holds them for three days or longer, prompting them to present to the pharmacy only when they need a dose. In this case, a review of the client’s dosing schedule may be advantageous to the client, pharmacist and prescriber. Clients who attend erratically for doses have a reduced likelihood of achieving good outcomes, and a review of the client’s dose and regime is recommended in these circumstances (Lintzeris et al 2006).

The recommended recommencement doses of buprenorphine are summarised in Table 13.
Table 13: Recommended recommencement doses of buprenorphine (with or without naloxone)

<table>
<thead>
<tr>
<th>Usual 24-hour buprenorphine dose</th>
<th>Recomencement dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>More than 8 mg</td>
<td>8 mg if less than seven days with no dose</td>
</tr>
<tr>
<td></td>
<td>4 mg if seven or more days with no dose</td>
</tr>
<tr>
<td>6–8 mg</td>
<td>6–8 mg</td>
</tr>
<tr>
<td>2–4 mg</td>
<td>2–4 mg</td>
</tr>
</tbody>
</table>


Clients can be brought up to their usual maintenance dose over subsequent days (using the dosing increments discussed earlier) if the prescriber and client think this is appropriate (Lintzeris et al 2001a).

Transfer from buprenorphine (with or without naloxone) to methadone

Transferring from buprenorphine (with or without naloxone) to methadone is easier than transferring from methadone to buprenorphine (with or without naloxone).

The following summary has been adapted from the Australian National Clinical Guidelines and Procedures for the Use of Buprenorphine in the Treatment of Opioid Dependence (Lintzeris et al 2006).

A transfer to methadone should be considered when:

- the client experiences intolerable side effects with buprenorphine
- the client has an inadequate response to buprenorphine treatment
- buprenorphine is not available
- the client is in early pregnancy or intends to become pregnant (see ‘Pregnancy and lactation’, page 41, for more information)
- the client experiences complications with opioid antagonists and analgesics (in clients who have frequent overdoses buprenorphine can complicate resuscitation efforts with naloxone, and for clients who require frequent opioid analgesia due to recurrent acute or chronic pain full agonists (eg, methadone) may be more stabilising), see ‘Pain Management’, page 46, for more information
- the prescriber is concerned the client may be diverting buprenorphine.

Methadone should be started when the client’s next opioid substitution dose is due. This means 24 hours after the last 24-hour dose or 48 hours after a 48-hour dose of buprenorphine. Evidence-based practice advises that the initial maximum daily dose of methadone should be no more than 40 mg (see Table 14).
Table 14: First methadone dose after transfer from buprenorphine (with or without naloxone)

<table>
<thead>
<tr>
<th>Buprenorphine (with or without naloxone) dose</th>
<th>First methadone dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 mg or less</td>
<td>20 mg or less</td>
</tr>
<tr>
<td>6 mg or more</td>
<td>40 mg</td>
</tr>
</tbody>
</table>

Increases to the methadone dose should take into account buprenorphine’s long duration of action. Titration should not occur too quickly as buprenorphine can diminish the effects of methadone for several days. Allow enough time for buprenorphine to ‘wash out’ before giving the client significant increases in methadone dose.

Medical withdrawal from buprenorphine substitution treatment

Reducing from buprenorphine (with or without naloxone) substitution treatment is a major step in the treatment pathway. It should be attempted only after a period of substitution treatment and psychosocial stabilisation where the client has been abstinent from other illicit drug use, has a stable supportive environment and has no added foreseeable pressures.

Significant opioid withdrawal during a medical reduction is unusual if the dose is tapered. The reduction in dose should be carefully planned with the client to optimise the chance of a successful completion. Reductions should be realistic, as gradual incremental reductions achieve higher success rates than do rapid reductions.

See ‘Opioid Withdrawal using Buprenorphine (with or without naloxone)’, page 51, for more information.

Clients should be prepared to expect some withdrawal discomfort once they reach lower doses.

Table 15 summarises general rates of dose reduction, although reductions may occur more rapidly or more slowly.

Table 15: Dose reduction rates when reducing from buprenorphine (with or without naloxone)

<table>
<thead>
<tr>
<th>Dose of buprenorphine (with or without naloxone)</th>
<th>Reduction rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>More than 16 mg</td>
<td>4 mg per week or fortnight</td>
</tr>
<tr>
<td>8–16 mg</td>
<td>2–4 mg per week or fortnight</td>
</tr>
<tr>
<td>Less than 8 mg</td>
<td>2 mg per week or fortnight</td>
</tr>
</tbody>
</table>

An alternative regimen is set out in Table 16.
Table 16: Gradual dose taper schedule of buprenorphine (with or without naloxone)

<table>
<thead>
<tr>
<th>Week</th>
<th>From 20 mg of buprenorphine</th>
<th>From 16 mg of buprenorphine</th>
<th>From 8 mg of buprenorphine</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>16 mg</td>
<td>12 mg</td>
<td>8 mg</td>
</tr>
<tr>
<td>2</td>
<td>8 mg</td>
<td>8 mg</td>
<td>4 mg</td>
</tr>
<tr>
<td>3</td>
<td>4 mg</td>
<td>4 mg</td>
<td>4 mg</td>
</tr>
</tbody>
</table>


A temporary halt in the dose reduction process with a possible increase in dose may be warranted if the client:
- lapses and uses illicit opioids or other drugs
- experiences a deterioration in their physical, psychological or social wellbeing
- experiences added pressure or stress from external factors.

Managed withdrawal alone is not sufficient for long-term opioid-dependent clients since relapses are common following the completion of treatment. Other treatment strategies should be put in place before the client completes their buprenorphine treatment (Ling 2002).
Administration and Dispensing of Buprenorphine (with or without naloxone)

General information

Buprenorphine (with or without naloxone) is a sublingual tablet designed to be placed under the client’s tongue until the dose is absorbed. It has poor bioavailability if swallowed.

The sublingual absorption of buprenorphine is highly dependent on the length of time the drug is in contact with the oral mucosa, and ensuring clients understand this is important. Giving clients whole tablets ensures the most gradual absorption but these can be diverted more easily than tablets which have been broken into smaller pieces (Lintzeris et al 2006).

The tablet can take 2–10 minutes (depending on the size of the dose) to dissolve, so requires a longer period of supervised consumption than does methadone (Muhleisen et al 2003). The tablet will dissolve and be absorbed more quickly if the tablets are crumbled into smaller pieces (but not crushed into a powder).

If the tablets are crumbled, the daily average dose for buprenorphine does not need to increase (Muhleisen et al 2003). This process can be used if clients are suspected of not taking the full dose at the pharmacy and saving some or all of the dose for later misuse or diversion.

Crushing the tablets into a fine powder is not recommended, because some of the dose may be lost in the client’s saliva when swallowed.

Crumbling the tablets is not a replacement for pharmacists being vigilant when administering buprenorphine. The stages in Table 17 should be followed to minimise the risk of diversion or misuse. See also ‘Diversion and misuse’, page 39.
**Table 17:** Process to minimise the risk of diversion or misuse

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>The pharmacist should ask to see inside the client’s mouth prior to giving the dose. Any gum or lollies should be removed.</td>
</tr>
<tr>
<td>2</td>
<td>The pharmacist can give the client a bitter-tasting drink such as lemon cordial prior to administering the medication to increase salivation and dissolution, which will speed up the absorption of the tablets.</td>
</tr>
<tr>
<td>3</td>
<td>The pharmacist should place the tablets in a small container, so the client can put them in their mouth without handling them.</td>
</tr>
<tr>
<td>4</td>
<td>If the client finds it uncomfortable to put all the tablets under their tongue at once, they should absorb two tablets at a time (one under each side of their tongue).</td>
</tr>
<tr>
<td>5</td>
<td>The pharmacist should check the client’s mouth after they have placed the tablets under their tongue to ensure the medication is in the correct position in the mouth for absorption to occur.</td>
</tr>
<tr>
<td>6</td>
<td>The client should be informed of the length of time necessary for absorption to occur (three to five minutes for most of the dose to be absorbed) and advised to try not to swallow their saliva during this time.</td>
</tr>
<tr>
<td>7</td>
<td><strong>If the pharmacist ...</strong></td>
</tr>
<tr>
<td></td>
<td>can supervise the client directly</td>
</tr>
<tr>
<td></td>
<td>cannot supervise the client directly until the tablet has dissolved</td>
</tr>
<tr>
<td>7</td>
<td>The pharmacist should check inside the mouth of the client prior to them leaving the site to ensure the tablet has completely dissolved.</td>
</tr>
</tbody>
</table>

**Clients presenting intoxicated**

If a client presents intoxicated from any drug they cannot be administered their dose of buprenorphine (with or without naloxone). However, to reduce disruption in the pharmacy, they may re-present later in the day and be administered their dose if they are no longer intoxicated.

The prescriber must be notified of the client’s intoxication before administering the client’s next dose. If intoxication occurs repeatedly, the prescriber will review the client’s treatment including any takeaway arrangements.

**Incorrect dose administered**

The risks associated with an incorrect dose of buprenorphine (with or without naloxone) are not as severe as those with other opioid medications.
If a higher incorrect dose is administered (Lintzeris 2001a):

- the dispensing pharmacist should immediately notify the client and prescriber of the error
- the dispensing pharmacist should warn the client of the possible consequences (increased sedation or drowsiness for several hours) and warn them against additional drug use, and driving or operating machinery for the rest of the day
- trained health professionals or staff in a hospital accident and emergency department should monitor the client for at least 6 hours after the dose if the client:
  - is sedated after the dose
  - is new to substitution treatment (i.e., is within the first two weeks of treatment)
  - has a usual daily dose of buprenorphine (with or without naloxone) of 4 mg or less and was administered a dose of 16 mg or more
  - was administered a dose of buprenorphine (with or without naloxone) of 64 mg or more (regardless of the client’s routine daily dose).

The prescriber should review the client before their next dose of buprenorphine (with or without naloxone).

The client may require a lower dose the following day (in effect a two-day dose has been administered) or no dose.

If a lower incorrect dose has been administered the dispensing pharmacist should:

- notify the client immediately and ask them to return to the pharmacy that day for the remainder of the dose
- contact the prescriber and inform them of the error, so they can record it.

Diversion and misuse

All clinicians involved in a client’s care are responsible for minimising the risk of diversion, because diversion does not promote the rehabilitation of a person who is in treatment. New Zealand has a history of misuse of buprenorphine (with or without naloxone) and strong evidence from around the world exists of buprenorphine tablets being diverted.

The extent of diversion is proportional to the level of observation of the client when they are taking their tablets. Therefore, all doses administered must be under direct observation.

The risk of diversion and misuse are increased because buprenorphine (with or without naloxone) is in a solid form. Tablets take a longer time to administer than liquid methadone and can be more easily spat out and secreted for later diversion to the black market or misuse (sublingually or intravenously).
Diversion and misuse can cause adverse consequences.

- If the drugs are injected, risks are associated with injecting (eg, thrombophlebitis, infections from bacteria and fungi, the blockage of small veins with pieces of tablets, and blood-borne viruses from shared injecting equipment).
- The client may not stay in treatment. Clients not taking their dose as prescribed may experience unstable plasma levels, resulting in increased illicit drug use, destabilisation, and disengagement from treatment.
- Increased risk of overdose. Clients misusing combinations of drugs (especially sedating drugs) and people not prescribed buprenorphine (and who have little or no tolerance of opioids) are at a greater risk of overdose.
- Increased likelihood of opioid withdrawal, because both buprenorphine and naloxone will displace other opioids from the receptors (and may result in precipitated withdrawal in methadone-dependent people).

However, buprenorphine (with or without naloxone) does have the advantage being unlikely to cause a fatal overdose if taken without any other central nervous system depressants.

If diversion or misuse is suspected, the person administering the buprenorphine should crumble the tablets into granules (but not into a powder) to reduce the possibility of the client diverting the tablets. This also reduces the tablets’ resale value, which also discourages diversion (Muhleisen et al 2003).

If the prescriber suspects the client may be diverting or misusing the buprenorphine, they should instruct the pharmacist to crumble the tablets before administering them. The prescriber can write this on the prescription (preferred option) or issue a general direction to the pharmacist.

If diversion or misuse is ongoing, the prescriber must assess the client’s suitability for treatment with buprenorphine.

**Missed doses**

Missed doses should not be replaced. A single missed dose of buprenorphine is unlikely to cause adverse effects, because of the drug’s slow disassociation from and high affinity for the opioid receptor.

The pharmacist should contact the prescriber when a client on a less than daily dispensing regime attends for a dose on a ‘non-dosing’ day after a missed dose. The prescriber should instruct the pharmacist as to what dose to give the client. The pharmacist can not give a replacement or interim dose unless they have authorisation from the prescriber.

For more information on missed doses, see ‘Missed doses’, page 33.
Use in Special Populations

Pregnancy and lactation

Buprenorphine alone or with naloxone is contraindicated for use in pregnancy and not recommended during lactation. Prescribers should keep up to date with the latest research in this area, as evidence is growing to support the safe use of buprenorphine alone during pregnancy. However, no evidence exists for the safety of buprenorphine with naloxone in pregnancy.

Studies are being undertaken on the effects of buprenorphine during pregnancy and lactation in humans. There is growing evidence that the use of buprenorphine in pregnancy does not increase risks or differ significantly from the risks associated with the use of methadone or other opioids (Johnson et al 2003b).

When a pregnant woman uses buprenorphine alone, her baby is likely to experience no neonatal abstinence syndrome (NAS) or a mild case of NAS compared to that experienced with methadone (Kayemba-Kay’s and Laclyde 1998). This evidence has been gathered for buprenorphine alone, not buprenorphine in combination with naloxone. It is unknown how, if at all, naloxone when used as a daily medication affects a foetus.

Methadone remains the medication of choice for opioid substitution in pregnancy.

Buprenorphine is a category C drug

The United States’ Food and Drug Administration (FDA) and the Australian Drug Evaluation Committee (ADEC) list buprenorphine as a category C drug. A drug in this category indicates (Hale 2004, p 17):

‘Either studies in animals have revealed adverse effects on the foetus (teratogenic or embryocidal, or other) and there are no controlled studies in women, OR studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the foetus.’

Buprenorphine has been listed as a category L3 drug for breastfeeding (Hale 2004) which is defined as a moderately safe drug (Hale 2004, p 18).

‘There are no controlled studies in breastfeeding women; however the risk to untoward effects to a breastfed infant is possible or controlled studies show only minimal non-threatening adverse effects. Drugs should be given only if the potential benefit justifies the potential risk to the infant.’

Buprenorphine is present in breastmilk with an apparent milk to plasma ratio of approximately 1 but does not appear to suppress NAS (Johnson et al 2003a).
Opioid-dependent women wanting to become pregnant

Opioid-dependent women who want to become pregnant should be advised to consider methadone maintenance or alternative treatment to manage their dependence.

Opioid-dependent women not wanting to become pregnant

Contraception should be recommended to women not wishing to become pregnant (Lintzeris et al 2001a).

Any female client seeking maintenance treatment who might become pregnant should be counselled on the potential risks of buprenorphine (with or without naloxone) during pregnancy.

Becoming pregnant while on buprenorphine treatment

The following information has been adapted from the Australian National Clinical Guidelines and Procedures for the Use of Buprenorphine in the Treatment of Heroin Dependence (Lintzeris et al 2001a).

If a female client becomes pregnant while on buprenorphine treatment, her clinician should seek advice from a specialist unit providing obstetric and paediatric services for chemically dependent women and their babies.

Counselling should be provided to the woman about treatment options and she should be offered support before a choice of treatment is made.

Continuation of pregnancy and transfer to methadone substitution treatment

The preferred option for opioid-dependent women who become pregnant while on buprenorphine treatment and wish to continue with their pregnancy is to transfer to methadone substitution treatment. This is because no data exists on the safety of buprenorphine in combination with naloxone in pregnancy.

There is a potential risk to client stability during the transfer process. Clients on less-than-daily dosing should be transferred back to daily dosing with no dose changes for at least three days before transferring to methadone. Methadone should be started within 24 hours of the client’s stopping buprenorphine and after an assessment.

Clients should be monitored daily for the following three days, then regularly (eg, weekly) until stabilisation is complete.

A suggested transfer schedule is outlined in Table 18.
Table 18:  Suggested transfer schedule from buprenorphine (with or without naloxone) to methadone

<table>
<thead>
<tr>
<th>Last buprenorphine (with or without naloxone) dose</th>
<th>First methadone dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 mg or less</td>
<td>20 mg</td>
</tr>
<tr>
<td>More than 4 mg and less than 8 mg</td>
<td>30 mg</td>
</tr>
<tr>
<td>8 mg or more</td>
<td>40 mg</td>
</tr>
</tbody>
</table>


Clients using multiple or complex combinations of drugs or on doses larger than 16 mg of buprenorphine should be admitted to an inpatient unit for their transfer to methadone. This allows the mother and foetus to be observed closely for evidence of withdrawal and distress.

Continuation of pregnancy and buprenorphine (with or without naloxone) treatment
It is not recommended that an opioid-dependent woman who is pregnant and wishes to continue her pregnancy remains on buprenorphine with naloxone, because no information exists about its safety. However, evidence is growing that buprenorphine alone may be safe in pregnancy.

Clients wanting to remain on this treatment must be told of the risks of remaining on buprenorphine, that it is prescribed off licence, and that methadone has the most evidence of safe use during pregnancy.

For medication during delivery, see ‘Obstetric pain management’, page 47.

Termination of pregnancy
Women wishing to be considered for termination of their pregnancy should be referred to the appropriate services.

Neonatal monitoring
All neonates exposed to buprenorphine in utero should be monitored. Monitoring and treatment of buprenorphine-NAS is identical to that for methadone-NAS.

NAS can occur in all babies born to opioid-dependent mothers. It is unrelated to the maternal opioid dose.

NAS can start within 12–48 hours after delivery but it can be delayed for up to several weeks. Additional medication such as benzodiazepines can delay the onset of NAS.

Evidence is showing that buprenorphine is associated with a reduced severity of NAS in buprenorphine-dependent babies.

For more detailed information, read Clinical Guidelines for the Use of Buprenorphine in Pregnancy (Dunlop et al 2003).
**Buprenorphine (with or without naloxone) use with liver disease**

A significant number of people requiring opioid-substitution treatment have hepatitis, which causes some abnormality in their liver enzymes and possibly impaired liver function.

Buprenorphine is metabolised by N-dealkylation via the cytochrome P<sub>450</sub> pathway and by glucuronidation. The isoenzyme P<sub>450<sub>3A4</sub> is the major isoenzyme involved in buprenorphine metabolism and it is significantly reduced in severe chronic liver disease (Tegeder et al 1999).

Naloxone undergoes direct glucuronidation as well as N-alkylation (Reckitt Benckiser 2005). Glucuronidation is thought to be less affected by liver cirrhosis (Tegeder et al 1999).

Buprenorphine is metabolised by the liver, so its activity may be increased and/or extended in clients with impaired liver function.

Naloxone metabolism may be impaired in patients with hepatic failure. Lower initial doses and cautious titration of dosage may be required in patients with hepatic dysfunction (Reckitt Benckiser 2005).

Clients with hepatitis should be monitored with baseline and periodic liver function tests. Sublingual doses of buprenorphine do not adversely affect liver function. However, intravenous misuse (which has an estimated peak effect 150 times greater than sublingual administration) can trigger a decompensation in clients with hepatitis C (Johnson et al 2003b). Therefore, prescribers should be aware of the potential for liver toxicity associated with the intravenous misuse of buprenorphine, and ensure appropriate monitoring of clients known or suspected to be using buprenorphine intravenously (Johnson et al 2003b). Once intravenous illicit use stops, liver function tests improve.

**Buprenorphine hepatitis**

Liver function tests are advised during buprenorphine maintenance as an increase in aspartate aminotransferase levels may occur with increasing dose levels.

One study reports that after intravenous injection of buprenorphine a significant increase in aspartate aminotransferase was seen in four patients, three of whom had associated jaundice. The authors suggest that the higher concentrations of buprenorphine achieved in the blood after intravenous use could trigger hepatitis in some users, possibly in those whose liver function is already impaired by viral infections and/or other factors (Verrando et al 2005).

Clients should be warned of the potential risk of hepatitis occurring if they use buprenorphine intravenously.
Buprenorphine (with or without naloxone) use with HIV anti-retroviral therapy

Compliance with anti-retroviral therapy has been observed in HIV-positive clients maintained on buprenorphine (Moatti et al 2000).

However, research on the potential interactions between buprenorphine (with or without naloxone) with anti-retroviral medications is limited. Because buprenorphine is metabolised by the liver, it may interact with anti-retroviral medications (Johnson et al 2003b).

When inducting clients on to or altering their dose of buprenorphine (with or without naloxone) clinicians should, as standard practice, monitor clients for possible adverse effects or reduction in effect of all other medications they are taking.

Buprenorphine (with or without naloxone) use with renal disease

Buprenorphine is well tolerated in clients with renal disease. No significant differences exist in the pharmacokinetics of buprenorphine in opioid-dependent people compared with control populations. However, the concentrations of buprenorphine metabolites are higher in people with renal impairment (Johnson et al 2003b).

Buprenorphine (with or without naloxone) use with methadone-related prolongation of QTc interval

The cardiac safety of buprenorphine in clients with methadone-related QTc prolongation has not been described.

There is a report of a patient who developed Torsade de Pointes and who was found to have a significantly prolonged QTc interval on high dose methadone. His QTc interval returned to within normal limits after transfer to buprenorphine (Krantz et al 2005).
Pain Management

General pain management

It is more difficult to manage pain relief in clients on buprenorphine (with or without naloxone) than in clients on methadone treatment. The buprenorphine blockade on the opioid receptor at higher buprenorphine doses, means usual opioid pain-relief medications such as morphine may not provide the same effect or relief.

Clients on buprenorphine (with or without naloxone) have a diminished response to opioids prescribed for analgesia and are more sensitive to pain, so considerably higher opioid doses are needed for effective pain relief.

When considering pain relief for these clients, continue to prescribe buprenorphine (with or without naloxone) for opioid dependence, if possible.

Transfer the client to daily dosing if they are on less-than-daily dosing, then prescribe adequate pain relief. This is important, because clients have a history of discharging themselves from hospital if their pain relief is not adequately managed.

Prescribe analgesia in a step-wise manner starting with non-opioid analgesics such as paracetamol, aspirin and non-steroidal anti-inflammatory drugs or tramadol. Trial standard opioid analgesia for its effectiveness.

If analgesia is needed in specific sites, consider local anaesthesia.

If stronger pain relief is required, consider increasing the buprenorphine (with or without naloxone) dose temporarily as the ceiling effect on respiratory depression does not extend to its analgesic effect. This is the simplest option and can be achieved with doses of up to 32 mg daily.

For more severe pain that requires full opioid agonist analgesic medication, stop the buprenorphine as it will reduce the effectiveness of other opioid medication, because of its high affinity to the receptor, and titrate upwards a short-acting opioid medication such as morphine. Initial doses may be very large as the buprenorphine is still present, but monitor the morphine dose when the buprenorphine (with or without naloxone) is stopped as over-sedation and respiratory depression can occur when the buprenorphine detaches from the opioid receptors.

To recommence buprenorphine, induct in the usual way (see ‘Induction and stabilisation’, page 21). Liaise with the specialist acute pain service if the client is still in hospital.

Clients experiencing chronic pain that does not respond to increasing buprenorphine doses may find it beneficial to transfer to a full opioid agonist such as methadone.
Obstetric pain management

Suggested treatments for managing pain during delivery include (Dunlop et al 2003):

- non-pharmacological treatments (eg, showering, massage, mobilisation)
- transcutaneous electrical nerve stimulation during early labour
- nitrous oxide inhalation
- epidural anaesthesia for second- and third-stage pain relief
- spinal anaesthesia for second-stage pain relief
- pudendal block for low instrumental delivery
- local anaesthetic infiltration for episiotomy.

Caesarean pain relief includes spinal, epidural and general anaesthetics.

Pain relief after delivery includes paracetamol and non-steroidal medications.
Overdose Management

Results of opioid-related overdose
Opioid-related overdose results in depression of respiration causing hypoxia and death with pulmonary oedema as a complicating factor (White and Irvine 1999).

Buprenorphine appears to have less effect on respiratory depression than full agonists, because it produces dose-related decreases in the respiratory rate in the lower dose range, but no further reduction with increased doses (White and Irvine 1999).

It is thought that in an overdose, fewer mu opioid effects occur compared with those in a moderate or therapeutic dose, with a bell-shaped dose response curve occurring (Johnson et al 2003b). Reports describing patients taking 88 mg and 112 mg of buprenorphine at once describe symptoms of precipitated opioid withdrawal but not overdose (Clark et al 2002).

Overdose from poly-drug use more likely
Risk increases when buprenorphine is combined with other drugs (especially CNS depressants such as alcohol, benzodiazepines, barbiturates, tricyclic antidepressants and major tranquillisers). It seems that the protection from overdose caused by the ceiling effect no longer occurs when concomitant CNS depressants are abused. Overdose from poly-drug use is unlikely to be an opioid overdose and more likely from the other drugs taken such as benzodiazepines.

Several such deaths have been reported especially when buprenorphine and benzodiazepines have been injected together, so extra care should be taken when prescribing buprenorphine to benzodiazepine users. Benzodiazepines have been found in over 50 percent of cases of opioid overdose. It is thought to be linked to benzodiazepines exerting significant respiratory depression at high doses when combined with opioids (Reynaud et al 1998).

Overdose in children
Fatalities from accidental overdose in children are uncommon due to the poor bioavailability of buprenorphine taken orally. Children should be taken to hospital for monitoring regardless of the amount swallowed.

Treatment of opioid overdose
Naloxone is used for treating opioid overdose. Buprenorphine is not easily displaced from the opioid receptors making naloxone reversal more difficult than with methadone (Chadderton 2000).

In the case of overdose, much larger doses of naloxone (around 10–30 times the normal intravenous naloxone dose) may be required to reverse the effects of buprenorphine toxicity (Lintzeris et al 2001a).
The long action of buprenorphine should be taken into account (i.e., the blockade must be maintained for several hours or even days) (Chadderton 2000).

In the event of depression of respiratory or cardiac function:
- dial 111 and ask for the ambulance service
- carry out ABC (airway, breathing, circulation) techniques.
Urine Testing

Buprenorphine is not detected with routine urine toxicology screening.

Treatment services should discuss the development of a urine-screening test for buprenorphine with their local laboratory as appropriate.
Opioid Withdrawal Using Buprenorphine (with or without Naloxone)

Overview
People choose to withdraw from opioids for a variety of reasons and motivations. The goals of individual clients may vary considerably. Withdrawal should not be seen as a stand-alone treatment for achieving prolonged periods of abstinence, since research suggests withdrawal treatment alone has little, if any, long-term impact on levels of drug use.

Withdrawal from opioid medication can result in symptoms in the (O’Connor and Fiellin 2001):
- cardiovascular system (eg, tachycardia and hypertension)
- central nervous system (eg, pupil dilation, restlessness, irritability, insomnia and craving)
- gastrointestinal system (eg, nausea, vomiting and diarrhoea)
- skin (eg, piloerection)
- mucous membranes (eg, rhinorrhea and lacrimation).

The onset of symptoms is usually around 24–72 hours after the last 24-hour dose.

Symptoms peak around 3–5 days after short maintenance treatment (weeks or months) or 5–14 days after longer treatment.

Protracted withdrawal symptoms such as craving, sleep and mood disturbances can persist for weeks (Lintzeris et al 2001a).

A client’s withdrawal from opioids should be managed with supportive measures such as a safe environment, adequate nutrition and careful monitoring. Pharmacological therapies such as opioid and non-opioid medications should be available on request (O’Connor and Fiellin 2001).

Follow-up treatment should be discussed with the client before their managed withdrawal begins.

Opioid-based or symptomatic-relief medications have been used to reduce the discomfort of opioid withdrawal. Methadone has been used in tapering doses to reduce the severity of the withdrawal symptoms. However, methadone’s long half-life prolongs the process and adjunctive medications are usually required towards the end of the regimen. In addition, clonidine relieves only some of the symptoms that occur.
Lintzeris et al (2001b) summed up the advantages of buprenorphine by stating (on page 49):

‘Buprenorphine's pharmacological profile makes it an ideal treatment for heroin withdrawal, since it reduces cravings by exerting opioid effects, blocks the effects of additional heroin use, has a ceiling effect that increases its safety, is associated with minimal rebound withdrawal after short courses and facilitates a wide-range of continuing treatment options.’

The use of buprenorphine (with or without naloxone) in a managed withdrawal from opioids lessens the signs and symptoms of withdrawal and makes the process more comfortable and manageable for the client. However, buprenorphine does not eliminate all symptoms and the client should be prepared for some degree of discomfort during this time in order to reduce the likelihood of their dropping out of treatment.

All clients starting buprenorphine treatment should be in mild to moderate opioid withdrawal before being administered the first dose of buprenorphine and should be monitored for precipitated withdrawal.

**Comparison of buprenorphine with clonidine**

Most studies comparing buprenorphine to clonidine have been carried out in inpatient units.

Clonidine tends to suppress the autonomic signs and symptoms of withdrawal but is less effective for subjective symptoms (O’Connor and Fiellin 2001). Symptoms including myalgia, insomnia and nausea require other adjunctive medications to be prescribed.

Detoxification research has found buprenorphine superior to clonidine in reducing withdrawal severity (Lintzeris 2002) and in rates of completion of treatment. This applies to both inpatient and outpatient settings (Lintzeris et al 2006).

**Comparison of buprenorphine with tapered methadone doses**

The withdrawal process is easier with buprenorphine than with methadone (Chadderton 2000). The pharmacological characteristics of buprenorphine (ie, its slow dissociation from the opioid receptor and long duration of action) may positively affect detoxification regimens (Amass et al 1994).

Withdrawal seems to be milder during buprenorphine dose reductions, especially in the later half of the regimen, and the rate of buprenorphine dose-reduction can be more rapid than with methadone.

The symptoms and signs of withdrawal from buprenorphine are qualitatively similar to withdrawal from other opioids but the pattern of symptoms may be different, peaking earlier in buprenorphine-treated clients with little rebound withdrawal after treatment stops (Gowling et al 2004).
Methadone and buprenorphine appear to produce similar rates of completion of treatment (Lintzeris et al 2006).

**Slow or rapid buprenorphine-managed withdrawal**

Short regimens of buprenorphine-managed withdrawal have the advantage of covering the most severe part of the opioid withdrawal syndrome while minimising the rebound withdrawal phenomena and duration of withdrawal.

Rebound withdrawal has been associated with detox regimens of more than several days (ie, more than four to five days), and typically starts one to three days after the last dose of buprenorphine, with a peak at two to five days after the last dose and persistence of symptoms for several weeks (Lintzeris 2002).

Longer regimens of buprenorphine-managed withdrawal have the advantage of a more comfortable withdrawal with less severity in opioid-withdrawal symptoms and greater client retention in treatment.

More gradual reductions have been shown to provide longer periods of abstinence and higher rates of opioid negative urinalysis (Amass et al 1994).

**Inpatient- or outpatient-managed withdrawal**

Lintzeris (2002, p 39) differentiated between inpatient and outpatient withdrawal as:

‘The primary role of medication in inpatient settings is to relieve the more severe discomfort of withdrawal while the increased capacity for monitoring, supportive counselling, and a drug free environment facilitate the clients progress through withdrawal. In contrast the outpatient is exposed to regular cues and triggers for continued heroin use. Outpatient medication should not only relieve withdrawal discomfort; the dose should aim to reduce cravings for heroin use and to block (or at least reduce) the effects of ongoing heroin use during the withdrawal attempt.’

Inpatient regimens cost more than outpatient regimens. However, outpatient regimens should be carried out only in a supportive environment with uncomplicated cases and with symptomatic medications available if needed.

A client’s referral to an inpatient unit should be considered if they have (Lintzeris et al 2001a):

- an unstable medical or psychiatric condition
- a poly-drug dependence and are withdrawing from multiple drugs
- an unclear medical, psychiatric or drug-use history, which requires them to be closely monitored in a supervised unit
- an unsupportive home environment
- had a previous failure at an outpatient-managed withdrawal regimen.
Medical withdrawal in an inpatient setting

In this discussion, the doses of buprenorphine are regardless of whether naloxone is also present.

Because buprenorphine has an earlier peak in opioid withdrawal, inpatient stays can be shorter than with methadone withdrawal. It is still recommended that the client remains in the inpatient unit for monitoring for at least two to three days after their last buprenorphine dose.

Inpatient doses of buprenorphine can generally be lower than those required in outpatient regimes with 'as required' dosing. Outpatient withdrawal regimens are designed to block craving and use on top (Lintzeris et al 2001a).

The regimens can be fixed (eg, Table 19) or flexible (eg, Table 20), depending on the client’s needs and the inpatient unit’s capabilities. The dosing regimes outlined in Tables 19 and 20 are guides only; they are not the only managed-withdrawal schedules that can be used. Alter regimens according to the client’s need.

Score clients opioid-withdrawal symptoms and adjust their medication requirements accordingly.

Table 19: Fixed dosing schedules for buprenorphine (with or without naloxone) withdrawal in an inpatient setting

<table>
<thead>
<tr>
<th>Day</th>
<th>Buprenorphine (with or without naloxone) dose</th>
<th>Ten-day schedule (mg)</th>
<th>Seven-day schedule (mg)</th>
<th>Three-day schedule (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>8</td>
<td>8</td>
<td>12</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>6</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>4</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>4</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>4</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>6</td>
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<td>0</td>
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<td>7</td>
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<td>8</td>
<td></td>
<td>2</td>
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<td>9</td>
<td></td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td></td>
<td>0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 20: Flexible dosing schedule for buprenorphine (with or without naloxone) withdrawal in an inpatient setting

<table>
<thead>
<tr>
<th>Day</th>
<th>Buprenorphine (with or without naloxone) dose</th>
<th>Total daily dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4 mg at onset of withdrawal plus an additional 2–4 mg in the evening if required</td>
<td>4–8 mg</td>
</tr>
<tr>
<td>2</td>
<td>4 mg in the morning plus an additional 2–4 mg in the evening if required</td>
<td>4–8 mg</td>
</tr>
<tr>
<td>3</td>
<td>4 mg in the morning plus an additional 2 mg in the evening if required</td>
<td>4–6 mg</td>
</tr>
<tr>
<td>4</td>
<td>2 mg in the morning plus 2 mg in the evening if required</td>
<td>0–4 mg</td>
</tr>
<tr>
<td>5</td>
<td>2 mg if required</td>
<td>0–2 mg</td>
</tr>
<tr>
<td>6</td>
<td>No dose</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>No dose</td>
<td></td>
</tr>
</tbody>
</table>


Additional ‘when required’ doses should not be administered within four hours of the last dose and should be administered only if the client is in moderate to severe opioid withdrawal. Ideally, the evening dose should be administered between 5 pm and 10 pm.

Buprenorphine (with or without naloxone) should not be administered if the client has any symptoms of intoxication or sedation.

**Medical withdrawal in an outpatient setting**

In this discussion, the doses of buprenorphine are regardless of whether naloxone is also present.

It is good practice to aim to complete a client’s managed withdrawal regimen early in the week. This avoids a client finishing their regimen just before or during the weekend (when the client is not likely to have clinical support). Offer the client extra support in the first few days after they have completed their regimen and consider using extra adjunctive medications or additional doses of buprenorphine.

A greater amount of flexibility is required when dealing with an outpatient withdrawal as several external and internal factors may complicate the overall withdrawal process such as cueing and craving.

A doctor, pharmacist or nurse should review the client daily when they attend for supervised dosing.

The client’s objective and subjective withdrawal symptoms should be monitored and their doses adjusted if needed.

All outpatient doses should ideally be consumed daily under supervision.

Tables 21 and 22 are examples of outpatient regimens.
### Table 21: Example of outpatient withdrawal regimen, recommended upper and lower limits of buprenorphine (with or without naloxone)

<table>
<thead>
<tr>
<th>Day</th>
<th>Recommended upper and lower limits of buprenorphine (with or without naloxone) (mg)</th>
<th>Recommended buprenorphine (with or without naloxone) dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4–8</td>
<td>6</td>
</tr>
<tr>
<td>2</td>
<td>4–12</td>
<td>8</td>
</tr>
<tr>
<td>3</td>
<td>4–16</td>
<td>10</td>
</tr>
<tr>
<td>4</td>
<td>2–12</td>
<td>8</td>
</tr>
<tr>
<td>5</td>
<td>0–8</td>
<td>4</td>
</tr>
<tr>
<td>6</td>
<td>0–4</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>0–2</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Source: Reckitt Benkiser 2003

Some clients may require a longer regimen than that shown in Table 21. Table 22 is a 20–36-day flexible withdrawal regimen.

### Table 22: Example of 20 to 36 day outpatient withdrawal regimen from buprenorphine (with or without naloxone)

<table>
<thead>
<tr>
<th>Day</th>
<th>Equal reduction schedule from buprenorphine (with or without naloxone) (mg)</th>
<th>Fifty percent reduction schedule from buprenorphine (with or without naloxone) (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–4</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>5–8</td>
<td>14</td>
<td>8</td>
</tr>
<tr>
<td>9–12</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>13–16</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>17–20</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>21–24</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>25–28</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>29–32</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>33–36</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Source: Reckitt Benkiser 2003

**Supportive care and monitoring**

After becoming abstinent clients should be actively encouraged and supported to consider further treatment options to help them avoid returning to illicit drug use. Services should offer interventions such as groups to support clients who are undergoing withdrawal or who have completed withdrawal from opioid-substitution treatment.
Return to substitution treatment

If the client's managed withdrawal is unsuccessful, consider transferring them to maintenance treatment. Initiate titration onto a maintenance dose.
Case Management

For information about case management, see *Practice Guidelines for Opioid Substitution Treatment in New Zealand* (Ministry of Health 2008).
General Practitioner Prescribing of Buprenorphine (with or without Naloxone)

General practitioners who become involved in prescribing buprenorphine (with or without naloxone) to clients need to have adequate training in the pharmacological effects of buprenorphine and its appropriate use for managing opioid dependence.

General practitioners must be authorised by the local specialist service or be individually approved (Ministry of Health 2008: Appendix 2) to prescribe buprenorphine (with or without naloxone) for treatment of opioid dependence.
References


Glossary

Note: Italicised words in the definitions are included in the glossary.

absorption  The process of the drug's movement from the place it was administered into the systemic circulation.

affinity  A drug's action is affected by the degree of attraction (affinity) between it and its receptor on the cell's surface (ie, how strongly it binds to the receptor).

antagonist  A drug that binds to a receptor without eliciting a response, preventing the activation of the receptor by other drugs (ie it blocks the receptor).

bind  To form a chemical bond with.

bioavailability  The extent of drug absorption into the systemic circulation, which is dependent on the route of administration (eg the bioavailability of oral morphine is 50% compared with 100% for intravenous morphine).

ceiling effect  A plateau where further increases in dose result in no further increase in effect.

cross-tolerance  A phenomenon in which tolerance to one drug induces tolerance to another drug with similar pharmacology.

CYP<sub>450</sub>  See cytochrome <i>P</i><sub>450</sub> enzyme system.

cytochrome <i>P</i><sub>450</sub> enzyme system  The most important enzyme system of phase I metabolism. Drug interactions can occur when two drugs compete for the same enzyme at the same time, or when one drug causes an enzyme to increase its activity (induction) or decrease its activity (inhibition), altering the blood plasma levels of other drugs which are metabolised by the same enzyme.

distribution  After a drug enters the systemic circulation, it is distributed to the body's tissues. Distribution is generally uneven because of differences in blood perfusion, tissue binding, regional pH and the permeability of cell membranes.

distribution half-life  The time it takes for half of the amount of the drug to be distributed into the tissues.

diversion  The failure to consume medication on-site, and sell, swap or give it to others. (Injecting the medication or using it against medical advice is more strictly 'misuse' rather than diversion.)

elimination  The sum of the processes of drug loss (metabolism and excretion) from the body.

elimination half-life  The time it takes for half the amount of the drug to be removed from the body, which occurs after distribution, usually expressed as t½.

excretion  The process by which a drug or metabolite is eliminated from the body without further chemical change. See also elimination, metabolism.
first-pass metabolism

The process when part of the dose of a drug is metabolised by the gut wall or liver as it passes through the tissues to the systemic circulation. The extent to which individual drugs are affected by this varies (ie, some drugs are highly affected and others are not affected at all).

induction

The process of safely initiating and increasing the substitution medication up to an effective level.

intrinsic activity

The property of a drug that determines the amount of biological effect produced per unit of drug-receptor complex formed. Two agents combining with equivalent sets of receptors may not produce equal degrees of effect even if both agents are given in maximally effective doses; the agents differ in their intrinsic activities (ie, it is the degree to which the drug activates the receptor).

lipophilic

Able to be dissolved in lipids (fats).

metabolism

The sum of the processes of a wide range of chemical reactions, which are categorised as phase I or phase II, and which chemically modify the drug into further compounds, both inactive and active, in order for elimination to occur. The enzymes involved are present in many tissues but are generally more concentrated in the liver.

NAS

See neonatal abstinence syndrome.

neonatal abstinence syndrome

A syndrome characterised by specific symptoms in a newborn infant such as feeding problems, a high-pitched cry and increased muscle tone as a result of the mother’s dependence on drugs during pregnancy. It commences within 72 hours of birth and can last for up to several weeks.

peak

The highest or maximum concentration of a drug in the blood.

pharmacodynamics

The study of the biochemical and physiological effects of drugs and their mechanism of action.

pharmacokinetics

The study of how drugs move in the body (eg, the time it takes to be absorbed, how long it acts, how it is distributed in the body and how it is eliminated from the body).

pharmacotherapy

The treatment of a disease with drugs.

precipitated withdrawal

A phenomenon caused when a drug with a higher receptor affinity but a lower intrinsic activity displaces the drug currently occupying the receptor, resulting in a reduced biological effect and the experience of a physiological withdrawal syndrome by the individual.

receptor

A protein on a cell membrane or within the cell that binds to a specific substance and causes a specific response in the cell.

stabilisation

A multi-faceted condition that, at a minimum, means a person can cope on a consistent regular dose of medication without needing constant dose changes and reviews and can work consistently towards agreed goals.
<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>steady state</td>
<td>The point reached after a drug has been given for about five elimination half-lives and after which time any fluctuations in blood plasma levels will be consistent from one dosing period to the next, regardless of fluctuations within the dosing period.</td>
</tr>
<tr>
<td>sublingual</td>
<td>Beneath the tongue.</td>
</tr>
<tr>
<td>systemic circulation</td>
<td>The circulation of blood throughout the entire body.</td>
</tr>
<tr>
<td>takeaway</td>
<td>Any individually packed, daily dose of medication that is not consumed under observation.</td>
</tr>
<tr>
<td>therapeutic range</td>
<td>The range of blood plasma concentrations of a drug where an optimum outcome is expected.</td>
</tr>
<tr>
<td>titration</td>
<td>The process of increasing the medication dose over a period until stabilisation is reached.</td>
</tr>
<tr>
<td>trough</td>
<td>The concentration of a drug that occurs in the blood immediately before the next dose.</td>
</tr>
<tr>
<td>withdrawal</td>
<td>The discontinuation of the use of an addictive substance and the physiological and mental changes that accompany such discontinuation.</td>
</tr>
<tr>
<td>use on top</td>
<td>The use of illicit drugs on top of the use of a substitute medication.</td>
</tr>
</tbody>
</table>
Appendix A: Drug Interactions with Buprenorphine (with or without Naloxone)

Drug interactions listed for buprenorphine are typical of those listed for any opioid class of drug.

Cytochrome $P_{450}^{3A4}$ inhibitors

Increased levels of buprenorphine and norbuprenorphine can occur when buprenorphine is administered with other drugs that are metabolised via the cytochrome $P_{450}^{3A4}$ pathway. Monitor clients closely and consider reducing their dose. Other drugs include ketoconazole, protease inhibitors, calcium channel blockers, and macrolide antibiotics (Reckitt Benckiser 2005).

Cytochrome $P_{450}^{3A4}$ inducers

The interaction of buprenorphine with cytochrome $P_{450}^{3A4}$ inducers has not been investigated. It is recommended that clients should be closely monitored if inducers (eg, phenobarbital, carbamazepine, phenytoin, or rifampicin) are co-administered with buprenorphine (Reckitt Benckiser 2005).

Table 23 lists medications metabolised by cytochrome $P_{450}^{3A4}$. For an up-to-date list go to http://medicine.iupui.edu/flockhart/table.htm
Table 23: Medications metabolised by cytochrome P<sub>450</sub>3A4

<table>
<thead>
<tr>
<th>Substrates</th>
<th>Inhibitors</th>
<th>Inducers</th>
</tr>
</thead>
<tbody>
<tr>
<td>alfentanil</td>
<td>indinavir</td>
<td>amiodarone</td>
</tr>
<tr>
<td>alprazolam</td>
<td>methadone</td>
<td>chloramphenicol</td>
</tr>
<tr>
<td>amlodipine</td>
<td>midazolam</td>
<td>cimetidine</td>
</tr>
<tr>
<td>atorvastatin</td>
<td>nefludipine</td>
<td>ciprofloxacin</td>
</tr>
<tr>
<td>buspirone</td>
<td>ondansetron</td>
<td>clarithromycin</td>
</tr>
<tr>
<td>cafergot</td>
<td>pimozide</td>
<td>delavirdine</td>
</tr>
<tr>
<td>chlorpheniramine</td>
<td>progesterone</td>
<td>diethyl-dithiocarbamate</td>
</tr>
<tr>
<td>cisapride</td>
<td>quinidine</td>
<td>diltiazem</td>
</tr>
<tr>
<td>clarithromycin</td>
<td>quinine</td>
<td>erythromycin</td>
</tr>
<tr>
<td>cocaine</td>
<td>ritonavir</td>
<td>flunonazole</td>
</tr>
<tr>
<td>cyclosporine</td>
<td>salmeterol</td>
<td>gestodene</td>
</tr>
<tr>
<td>dapsone</td>
<td>saquinavir</td>
<td>grapefruit juice</td>
</tr>
<tr>
<td>dextromethorphan</td>
<td>sildenafil</td>
<td>indinavir</td>
</tr>
<tr>
<td>diazepam</td>
<td>simvastatin</td>
<td>itraconazole</td>
</tr>
<tr>
<td>diltiazem</td>
<td>tacrolimus</td>
<td>ketoconazole</td>
</tr>
<tr>
<td>domperidone</td>
<td>tamoxifen</td>
<td>mifepristone</td>
</tr>
<tr>
<td>erythromycin</td>
<td>terfenidine</td>
<td>nefazodone</td>
</tr>
<tr>
<td>estradiol</td>
<td>testosterone</td>
<td>nelfinavir</td>
</tr>
<tr>
<td>felodipine</td>
<td>trazodone</td>
<td>norfloxacin</td>
</tr>
<tr>
<td>fentanyl</td>
<td>triazolam</td>
<td>ritonavir</td>
</tr>
<tr>
<td>finasteride</td>
<td>verapamil</td>
<td>verapamil</td>
</tr>
<tr>
<td>haloperidol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>hydrocortisone</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note
* Although theoretical interactions may occur the significance of each drug interaction is unknown and may not be clinically significant due to cytochrome P<sub>450</sub>3A4 being the less dominant pathway.

Benzodiazepines

Buprenorphine (with or without naloxone) taken in combination with benzodiazepines may potentiate respiratory depression. Deaths have been reported when intravenous misuse of buprenorphine has occurred in conjunction with the use of benzodiazepines.

Alcohol

Alcohol taken with buprenorphine (with or without naloxone) increases the risk of overdose, including death.
Other CNS depressants

Buprenorphine (with or without naloxone) used with other CNS depressants (eg, other opioid derivatives, sedative H1 receptor antagonists, barbiturates, tranquillisers, phenothiazines, sedative/hypnotics, anxiolytics, neuroleptics) including alcohol may have an additive effect on central nervous system depression.

Use of buprenorphine with monoamineoxidase inhibitors, including up to two weeks after their discontinuation, may cause exaggerated opioid effects.

Other pure opioid agonists

Buprenorphine (with or without naloxone) used with pure opioid agonists may precipitate opioid-withdrawal syndrome, because buprenorphine has a higher affinity for the opioid receptor than other opioids.

Opioid antagonists

Opioid antagonists used with buprenorphine (with or without naloxone) may result in precipitated opioid-withdrawal syndrome.

Interaction data for buprenorphine is limited, but because it follows a similar metabolic pathway to that of methadone, it may interact with the same compounds as methadone (eg, enzyme inducers and inhibitors).
Appendix B: Medications to Relieve the Symptoms of Opioid Withdrawal

The medications listed in Table 24 may relieve the symptoms of opioid withdrawal.

Table 24: Medications to relieve symptoms of opioid withdrawal

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Medication</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tachycardia, sweating, tremor, anxiety</td>
<td>Clonidine**</td>
<td>75–150 mcg orally when required up to every six hours</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>Metoclopramide</td>
<td>10 mg orally when required up to three times a day</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>Loperamide</td>
<td>Two capsules initially, then one capsule with each loose bowel motion; up to eight capsules per day</td>
</tr>
<tr>
<td>Sleep disturbance</td>
<td>Zopiclone</td>
<td>7.5 mg at night for a short time (eg, three days) if particularly problematic</td>
</tr>
<tr>
<td>Headaches and general aches</td>
<td>Paracetamol, Ibuprofen</td>
<td>1 gram when required up to four times a day 400 mg up to four times a day</td>
</tr>
<tr>
<td>Leg cramps</td>
<td>Quinine</td>
<td>300 mg when required up to three times a day</td>
</tr>
<tr>
<td>Abdominal cramps</td>
<td>Hyoscine (Buscopan®)</td>
<td>20 mg when required up to four times a day</td>
</tr>
</tbody>
</table>

** Prescribing of clonidine: Although it is well researched internationally in the treatment of opioid withdrawal, clonidine is not registered for this use in New Zealand. Prescribers should be aware of the medico-legal implications of using clonidine in this context.

Clonidine has the potential to cause hypotension. Blood pressure should be measured prior to the first dose, and 30–60 minutes after the first dose to monitor the client’s response. If blood pressure falls to either 30 mmHg below baseline or less than 90 mmHg systolic, consider reducing the dose or stopping clonidine.

Rebound hypertension may occur if clonidine is stopped suddenly. This may be avoided by reducing the daily dose over three to four days prior to stopping.
Appendix C: Information for Clients

An information sheet about Suboxone® and treatment has been written by CADS, Auckland for clients and is reproduced on the following pages.

Reckitt Benckiser also provides written information for clients, which can be downloaded from http://www.medsafe.govt.nz/Consumers/CMI/CMIForm.asp.

Suboxone (Buprenorphine/Naloxone)

How Suboxone works

Suboxone contains Buprenorphine and Naloxone. Buprenorphine is the main ingredient. It’s a different type of opioid than heroin, morphine, methadone, etc, which are called full agonists; buprenorphine is a partial agonist and has what’s called a ‘ceiling effect’, ie, after a certain dose it produces no more effect, it’s just that the effect lasts longer.

Buprenorphine attaches itself/ ‘sticks’ to the opioid receptor in the brain more strongly than other opioids and will kick the others off the receptor. Because it holds onto the receptor and slowly leaches off, the withdrawal is smoother than withdrawing from methadone.

Naloxone is the drug used to bring people out of overdose (ie, Narcan). It’s been added to Suboxone to deter people from injecting. The naloxone has no effect when Suboxone is used as prescribed but if Suboxone is injected the naloxone puts you into withdrawal as it overrides the buprenorphine. Injecting Suboxone is like injecting naloxone.

Before taking Suboxone your body needs to be clear of all other opioids, including methadone. It’s best to wait as long as you can, even until you start experiencing the first signs of withdrawal, before your first Suboxone dose. If not, you may go into withdrawal. (See Precipitated Withdrawal.)

If you’re transferring from methadone to Suboxone your methadone dose will need to be reduced to around 30 mgs a day before your first Suboxone dose. You’ll be asked to wait until you are in mild to moderate withdrawal (you will probably know how long this takes to happen) before you get your first Suboxone dose. If you take it too early then you will get a precipitated withdrawal reaction.

The tablet is placed under the tongue until it is dissolved – this can take up from 2–10 minutes. Buprenorphine will not have much effect if you swallow it.

You will feel the effects within 30 to 60 minutes and the full effects after 1 to 4 hours. The duration of effects varies according to the dose and the person taking it. In general, the higher the dose, the longer the effects.
How Suboxone differs from methadone

Like methadone, Suboxone is designed to stop you feeling withdrawals and reduces the craving to use but for some people it has some possible advantages such as:

- not everyone likes taking methadone, so Suboxone gives you another alternative
- Suboxone gives you a feeling of being more clear-headed, less ‘cloudy’ than with methadone (though not everyone likes that clear-headed feeling)
- Suboxone is less dangerous in overdose if it’s taken as prescribed. Taking large doses of methadone can and has caused deaths; taking large doses of Suboxone won’t cause overdose and possible death IF it’s the only thing you’re taking. It’s because of the ceiling effect.

Suboxone as a withdrawal medication

If using Suboxone as a withdrawal medication, the physical effects of withdrawal are significantly easier to cope with and you’ll probably need less symptomatic relief medications compared to what you need when coming off methadone.

However, just because it may easier to come off opioids when using Suboxone, that doesn’t mean relapse doesn’t happen. Anyone can relapse regardless of what they’ve been using.

Suboxone as a substitution treatment

If using Suboxone as a substitution treatment, you’ll be started on daily dosing, and then you can move to less-than-daily dosing, eg, you might get double doses to take on Monday, a double dose to take on Wednesday and a triple dose to take on Friday. There’s no need for takeaway doses.

However, not everybody feels comfortable on this type of regimen.

Common side effects

Suboxone has a range of side effects similar to those of all opioids. Most side effects occur in the first week or two of treatment and settle down after that. Persistent side effects will stop when your treatment stops.

The most commonly reported side effects are:

- sleep problems (difficulty falling asleep and disturbed sleep)
- mood swings
- headaches are very common early in treatment but usually settle down in a few days
- constipation
- increased sweating (especially after exercise)
- tiredness or drowsiness (especially after a dose) which usually stops within days to weeks
- loss of appetite, nausea and vomiting (which usually stop after a few days)
• abdominal pain (cramps) which usually settle down quickly
• skin rashes and itching (which usually stop after a few days)
• tooth decay which is a problem associated with all opioids
• changes to menstrual cycle
• lowered sex drive
• respiratory depression especially when combined with other depressants such as alcohol or benzos. There have been reports of deaths of people who’ve injected the buprenorphine and taken benzos. Once you start mixing Suboxone with other drugs then the risk of overdose becomes the same as if you were taking methadone.

**Precipitated withdrawal**
Precipitated withdrawal happens when you still have a lot of opioids in your system. As Suboxone is a different type of opioid, it kicks the other ones off the brain’s opioid receptor and occupies the receptors itself. Because buprenorphine has weaker effects than morphine/methadone, this feels like a withdrawal reaction.

• Precipitated withdrawals typically happen 1–4 hours after the first Suboxone dose and last up to 12 hours.
• These withdrawals vary in intensity and generally consist of the usual: sweating, cramps, nausea, diarrhoea, anxiety and cravings.
• If the withdrawal symptoms are uncomfortable, the doctor can prescribe symptomatic relief so rather than using, let the doctor know this is happening.

**Other health issues**
You should not take Suboxone if you:
• have severe breathing problems
• have recent severe head injury
• have severe abdominal pain
• have a hypersensitivity to buprenorphine (get an allergic reaction)
• are pregnant.

**Hepatitis and liver problems**
Buprenorphine is an opioid and in general opioids do not cause problems for the liver; this includes hepatitis.

**Need to know more?**
If you have questions that aren’t answered here feel free to speak to the doctor.
Suboxone: A Guide to Treatment

Things you need to be aware of when taking Suboxone

Just like methadone, you do become dependent on Suboxone. If using it for substitution treatment, then you may notice if you miss doses but the withdrawal symptoms are less severe than with methadone. This is one of the reasons Suboxone is used at the end of a detox/withdrawal from opioids.

Suboxone has a blockade effect so using other opioids on top won’t have the desired effect. This is because the buprenorphine blocks the receptors in your brain so that other opiates like methadone, morphine and codeine can’t reach them, hence no effect.

Trying to override the blockade with larger amounts of drugs can significantly increase the risk of overdose because when the Suboxone wears off the effects of the other drugs kick in.

Suboxone interacts with other central nervous systems depressants including benzos (Valium/diazepam, temazepam, Rohypnol, etc), antidepressants, antipsychotics (mental health medications), and alcohol so you need to tell the prescriber if you’re taking any of these.

Although you can drink alcohol while taking Suboxone, be careful not to overdo it.

Suboxone is not designed for injection which can be painful and can cause tissue and vein damage which may lead to infection.

Hospitals may not stock Suboxone so it’s important to speak to your case manager about any planned hospital admissions.

If you end up in hospital unexpectedly, get the hospital staff to contact your prescriber who can provide the GP or hospital staff with guidance on pain management.

As yet there’s little research available about pregnancy and Suboxone. However, women are advised not to become pregnant while taking Suboxone.

If you do become pregnant, you’ll be transferred to methadone.

People requiring analgesia (pain relief) should preferably use non-opioid analgesics such as paracetamol, aspirin, and NSAIDs/non-steroidals like Voltaren and Nurofen, as opioid medications are less effective. Speak to the doctor about other options for severe pain.

If you have takeaway doses, store your buprenorphine safely out of the reach of children.

If you feel drowsy on buprenorphine it’s safest not to drive or operate machinery.
Suboxone comes in two different size tablets: one has 8 mg buprenorphine with 2 mg naloxone; the other has 2 mg buprenorphine with 0.5 mg naloxone. Your dose will be made up of a combination of these tablets.

The naloxone in the tablet has no effect (not absorbed) when taken sublingually (under the tongue). It is like taking buprenorphine alone.

Suboxone is lemon-lime flavoured.

The pharmacist/nurse may crumble the tablets to reduce the time you need to spend at the pharmacy. Crumbling decreases the time it takes for the dose to be absorbed and makes it easier if you need to take several tablets. Crushing the tablet to a fine powder is not recommended as you can accidentally swallow the powder.

Swallowing the tablet/s means the Suboxone will be less effective so it is important not to chew or swallow your dose.

**Information card for medical services**

If taking Suboxone as a substitution medication, you should carry an information card for emergency medical personnel telling them that you are on Suboxone.

Being on Suboxone changes the pain relief treatment options you can be given.

**Precipitated withdrawal**

When starting on Suboxone treatment it is important to make sure there are no other opioids in your system otherwise you can go into precipitated withdrawals as the Suboxone basically ‘kicks off’ the other opioids attached to the receptor, and your system has to adapt to a drug that’s a partial agonist (ie, it has less opioid activity than the other opioids such as heroin, morphine and methadone).

Precipitated withdrawals typically happen 1–4 hours after the first Suboxone dose and last up to 12 hours.

These withdrawals vary in intensity and generally consist of the usual: sweating, cramps, nausea, diarrhoea, anxiety and cravings.

If the withdrawal symptoms are uncomfortable, the doctor can prescribe symptomatic relief so rather than using, let the doctor know this is happening.

If you do use, it’ll be difficult to stabilise on Suboxone, plus you’ll continue to experience precipitated withdrawal symptoms.

Make sure you are in mild to moderate withdrawals before you have your first dose, otherwise you will be in worse withdrawals afterwards.
Tips for Suboxone dosing

Sublingual tablets like clean and moist mouths. To make absorption easier:

- avoid smoking, toothpaste or mouthwash, coffee or cola immediately before taking your dose as these can dry out your mouth
- bitter drinks (eg, citrus), water or chewing gum increase saliva production.

A step-by-step guide

- Place the Suboxone directly under your tongue. It will take from 2 to 10 minutes to dissolve.
- For the first few minutes try not to talk as you may accidentally swallow your dose.
- If you feel like the tablet is moving from under your tongue or you can taste it, don’t panic. Try gently tipping your head forward to move the tablet back in place.
- Try to distract yourself. Sometimes when we focus on not swallowing it increases the urge to do so. Try to relax and let the tablet dissolve.
- Make sure the tablet has dissolved before drinking anything.
- If you swallow your dose, tell the pharmacist or doctor.

Need to know more?

If you have questions that aren’t answered here feel free to speak to the doctor.