

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

Abbreviated version

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National Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Dependence:
Abbreviated Version

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Introduction

These guidelines have been prepared to aid medical practitioners in the safe and effective use of buprenorphine for the treatment of opioid dependence. Further exploration of these issues can be found in the full guidelines. (Clark et al 2006, National Clinical Guidelines and Procedures for the Use of Buprenorphine in the Treatment of Opioid Dependence. Canberra: Commonwealth of Australia.)

These guidelines were prepared under the auspices of the National Expert Advisory Committee on Illicit Drugs (NEACID), and endorsed by the Royal Australian College of General Practitioners (RACGP), the Australasian Professional Society on Alcohol and Other Drugs (APSAD), and the Royal Australasian College of Physicians (RACP). The work to prepare the guidelines was funded by the Commonwealth Department of Health and Ageing.

These guidelines are based on international research literature and clinical experience with the use of buprenorphine in Australia.

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

Two sublingual buprenorphine preparations are currently registered in Australia for treating opioid dependence within a framework of medical, social and psychological treatment. The mono product (Subutex®) is available as tablets containing 0.4, 2, or 8 mg buprenorphine. The buprenorphine-naloxone combination product (Suboxone®) is available as tablets contain both buprenorphine hydrochloride and naloxone hydrochloride in dosages of 2mg buprenorphine and 0.5mg naloxone, or 8mg buprenorphine and 2mg naloxone.

1 Clinical pharmacology

Buprenorphine is a synthetic opioid derived from the morphine alkaloid thebaine. It is a partial opioid agonist with high affinity for μ opioid receptors.

Buprenorphine is effective in the treatment of heroin dependence because:

- it substitutes for heroin, preventing the emergence of opioid withdrawal symptoms and reducing cravings;
- it diminishes the effects of additional opioids (e.g. heroin) due to prolonged occupancy of a high proportion of opioid receptors, blocking the action of heroin;
- it is long-acting, allowing daily (or less than daily) dosing.

Other relevant properties:

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

Withdrawal from buprenorphine

Withdrawal symptoms on stopping treatment may be milder than with other opioids (e.g. morphine). Typically, withdrawal from maintenance buprenorphine emerges three to five days after the last dose, with some features potentially lasting up to several weeks.

Side effects

- Similar to other opioids, the most common being constipation, disturbed sleep, drowsiness, sweating, headaches, nausea and reduced libido.
- Most prevalent in the initial treatment period.
- High doses are well tolerated and rarely induce clinically significant respiratory depression, even in individuals with low tolerance to opioids. However, there have been some reports of acute hepatitis following very high doses (>32mg iv).

Drug Interactions

- Other sedatives. Buprenorphine in combination with other sedative drugs (e.g. alcohol, benzodiazepines) can result in respiratory sedation, coma and death.
- Opioid antagonists. Very high doses of naloxone (e.g. 10 to 35 mg) may be required to partially reverse buprenorphine effects. Because of the uncertain response to naloxone, prolonged ventilatory support may be required in overdoses involving buprenorphine. Naltrexone can precipitate opioid withdrawal in patients on buprenorphine (although the effect may be delayed for up to 8 hours).
- Opioid agonists. Buprenorphine exerts a degree of blockade on the effects of full agonist opioids, which may complicate the use of opioids for analgesia. The initial dose of buprenorphine can precipitate opioid withdrawal in patients who have recently used an opioid drug.

Buprenorphine-naloxone combination product (Suboxone®)

The combination product was developed to limit the abuse potential of buprenorphine by reducing the potential for injection. The addition of naloxone does not alter the sublingual bioavailability of the buprenorphine.

When taken sublingually, the buprenorphine-naloxone combination product will act as if it was buprenorphine alone, with no apparent effect from the naloxone. If the buprenorphine-naloxone combination is injected, naloxone is likely to attenuate the effects of buprenorphine in the short term and is also likely to precipitate withdrawal in opioid-dependent individuals on full opioid agonists.

2 Regulatory requirements

Buprenorphine is an S8 medication.

- A medical practitioner must be authorised by the relevant jurisdictional body to prescribe buprenorphine.

Refer to the full national buprenorphine policy and your jurisdictional policy for the necessary requirements.

3 Indications, contraindications, precautions

A comprehensive assessment by an authorised prescribing doctor is essential.

Indications

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

- opioid-dependent;
- 16 years of age or more (a second or specialist opinion should be sought for individuals under 18);
- able to provide proof of identity (check the requirements in your jurisdiction for treatment with S8 medications);
- able to give informed consent to treatment.

Contraindications

- known hypersensitivity and/or severe side-effects from prior exposure to buprenorphine or Suboxone®.
- pregnancy or breast-feeding (see full guidelines for detailed discussion of this issue).
- severe respiratory or hepatic insufficiency.

Precautions

Particular caution should be exercised in prescribing for patients with:

- polydrug use (especially with sedative drugs);
- concomitant medical conditions including recent head injury; compromised respiratory function, acute abdominal conditions, severe hepatic disease;
- concomitant severe psychiatric condition;
- chronic pain;
- low or uncertain levels of neuroadaptation to opioids.

4 Prescribing guidelines for maintenance treatment

Initial buprenorphine dose: inducing heroin users

The first dose of buprenorphine should be administered when the patient is experiencing early features of opioid withdrawal, typically 6 to 12 hours, after the last heroin use (or longer if the patient has been using slow-release oral morphine) to reduce the risk of precipitated opioid withdrawal.

Rapid dose induction may be associated with better retention in treatment. An appropriate dose to achieve on the first day is 6 to 8mg. This may be given as a single dose or, if resources permit, in two doses, four hours apart, to reduce the risk of precipitated withdrawal and adverse effects. Prescribers should aim to achieve 12 to 16mg/day by day three.

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

- time since last opioid use, and whether long acting opioids such as slow-release oral morphine or methadone have been taken recently;
- perceived likelihood of continued alcohol, sedative drug (particularly benzodiazepines), or illicit drug use (low initial buprenorphine doses, with frequent reviews are warranted);
- concurrent medical conditions (see precautions) may also warrant the use of lower initial doses.

Initial buprenorphine dose: transferring from methadone maintenance treatment

Transfers should be planned, considered and monitored. If they result in destabilization, return to methadone treatment may be the best option.

Patients should be on a methadone dose of less than 40mg (and preferably 30mg or less) for at least one week prior to receiving their first dose of buprenorphine.

The first dose should be administered when the patient is experiencing a mild degree of methadone withdrawal. This will usually be at least 24 hours after the last dose of methadone.

The preferred approach for dose induction is repeated doses of 2 to 4mg given four hours apart, according to individual responses to the first dose.

The mono preparation (Subutex®) is the preferred formulation to administer following methadone to avoid any risk of withdrawal that might be precipitated by even very small amounts of naloxone that might be absorbed from the combination product (Suboxone®).

Transfer from higher doses (>40mg methadone) is difficult in an outpatient setting.

Stabilisation

Regular patient reviews are required in the first few weeks. Adequacy of dose, withdrawal symptoms, side effects, any additional drug use should be considered, and the dose adjusted as indicated by these reviews.

Maintenance buprenorphine dose levels should be achieved within one to two weeks of commencing buprenorphine. Daily dosing is recommended during the stabilisation period.

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

Decrease the dose if:

- features of intoxication with buprenorphine (e.g. sedation), particularly at peak effect times (1 to 4 hours after dosing);
- severe or intolerable side effects occur.

Increase the dose if:

- features of withdrawal over preceding 24 hours, increasing in the period immediately prior to the next dose;
- no features of intoxication to buprenorphine, particularly at peak effect times;
- heroin use or craving;
- nil or mild and tolerable side effects.

Maintenance treatment

Evidence suggests that most people will be able to be maintained on doses between 12 and 16mg daily. Doses of 4mg or less will not be as effective in retaining patients in treatment or reducing heroin use.

Frequency of dosing

The dose dispensed for a 48-hour period is initially double the normal daily (24 hour) buprenorphine dose, and the dose for three-times-a-week dosing is three times the normal 24-hour dose, to a maximum of 32mg/day. While doses higher than 32mg have been used, the registration of buprenorphine in Australia specifies a maximum dose of 32mg.

If a patient cannot be stabilized on reduced frequency dosing regimes due to the onset of withdrawal, cravings, side effects or features of intoxication, they should be returned to a more frequent dosing regime. It is expected that less than half of patients will prefer supervised alternate day dispensing to daily supervised dispensing.

Unsupervised doses

There are both benefits and problems associated with unsupervised dosing, and particular care should be exercised by prescribers in authorising them. The policy for unsupervised dosing of buprenorphine is determined by each Australian jurisdiction. Prescribers should check with the relevant authority in their jurisdiction to determine whether there is a preference as to which formulation of buprenorphine is used for unsupervised dosing.

Ancillary services / interventions

All patients should be actively encouraged to avail themselves of psychosocial services such as counselling.

Addressing continued high-risk drug use

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

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

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

Missed doses

Patients who repeatedly miss doses should be reviewed by their prescribing doctor to find out why and whether these issues can be addressed.

Patients who have missed more than one week of dosing should be re-inducted onto buprenorphine treatment, provided they are not intoxicated with opioids, alcohol or benzodiazepines. Those who have missed less than one week can be continued on their maintenance dose.

Cessation of buprenorphine maintenance treatment

Withdrawal from buprenorphine treatment: Research evidence regarding the nature and severity of withdrawal following cessation of buprenorphine maintenance treatment remains limited. A gradual dose reduction as indicated in the table below is recommended:

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

The patient should be assured that the rate of reduction can be changed in the event of difficulties e.g. intolerable withdrawal, stressors, or resumption of regular opiate use. An increase in heroin or other drug-use, or a worsening of the client's physical, psychological or social well-being, may warrant a temporary cessation or slowing-down of the reduction rate. Some clients will request doses of less than 2mg. Reductions of 0.4 to 0.8mg per week or fortnight may then be appropriate, especially for withdrawal from longer-term maintenance buprenorphine.

Commencing naltrexone

Some patients may wish to commence naltrexone as a relapse-prevention agent following buprenorphine maintenance treatment. To minimize the risk of withdrawal symptoms, naltrexone should be delayed for five to seven days after the last buprenorphine dose. Doses of naltrexone taken earlier than this may induce some withdrawal symptoms. If transfer to naltrexone is required in less than five days, advice should be sought from a specialist service.

Transfer to methadone maintenance treatment

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

5 Guidelines for the management of heroin withdrawal

The non-pharmacological management of heroin withdrawal should include:

- assessment and treatment matching;
- planning for withdrawal;
- supportive care (including provision of information and supportive counselling); and
- links to further treatment and support.

Prescribing and administering buprenorphine for heroin withdrawal

Delay first dose until the patient is experiencing early features of opioid withdrawal, generally at least 6 hours after last heroin use, 12 hours or more after last use of slow-release oral morphine.

Titrate doses against the patient's experience of withdrawal severity, cravings, side-effects and other drug use.

Attempt a short-term (4 to 5 day) regime but schedule a review of progress within a few days. Longer-term maintenance substitution treatment (with buprenorphine or methadone) should be recommended to patients who:

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

Inpatient withdrawal regimes: Modify inpatient regimes according to:

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

The following regime is recommended for an admission time of approximately one week.

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

Ancillary medications: Because buprenorphine is effective in reducing most withdrawal symptoms, other withdrawal medications are not routinely required. Where sleep is a problem, it is safer to increase the dose of buprenorphine than to prescribe benzodiazepines, with non-pharmacological approaches being encouraged. The use of high doses of benzodiazepines in combination with buprenorphine can result in overdose.

Transition to post-withdrawal treatment: Withdrawal alone has limited long-term benefits, and all patients attempting withdrawal should be encouraged to pursue ongoing drug treatment. Options include:

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

6 Complications or adverse events with buprenorphine treatment

The reported side effects of buprenorphine are similar to those of other opioids used in maintenance treatment. The most common adverse event reported in trials has been opioid withdrawal symptoms. Other side effects (in order of decreasing incidence) are headache, constipation, insomnia, asthenia, somnolence, nausea, dizziness, and sweating.

Most adverse reactions to buprenorphine are mild, well tolerated, and typically occur early in treatment with symptoms subsiding over time. However, there have been some reports of acute hepatitis following very high doses (>32mg iv).

Intoxicated presentations

Intoxicated patients should not be dosed with buprenorphine, and patients should be made aware of this prior to the commencement of treatment.

Incorrect dose administered

The risks associated with an incorrect dose of buprenorphine are not as severe as with full opioid agonist medications. In the event of an incorrect dose of buprenorphine being administered, refer to the detailed guidelines for recommended procedures.

Diversion of buprenorphine

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

Analgesia requirements for patients on buprenorphine

If acute pain cannot be managed by simple analgesics, tramadol, or increased doses of buprenorphine, advice should be sought from a specialist addiction or pain service. If chronic pain cannot be managed with simple non-opioid or weak opioid analgesics, tramadol or increased doses of buprenorphine, transfer to a stronger agonist such as methadone should be considered.

Patients being admitted for major surgery should indicate to their doctors that they are taking buprenorphine and discuss pain management options.

Pregnancy and lactation

Methadone maintenance is the first line treatment of opiate dependence in pregnancy. The key issue for women who want to remain on buprenorphine during pregnancy or breastfeeding is that they understand that the safety and effectiveness of buprenorphine has not yet been fully evaluated. Given the lack of knowledge of the effects of chronic use of naloxone in pregnancy, use of the combination product (Suboxone®) is not recommended. Only small amounts of buprenorphine and buprenorphine-naloxone pass into breastmilk. The potential risks of buprenorphine should be balanced with the overall positive effects of breastfeeding. Consultation with a specialist paediatric unit is advised.

