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Complications or adverse events with buprenorphine treatment

5.1 Side effects

Similar to those of other opioids

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

Most common is opioid withdrawal

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

TABLE 9: COMMONLY REPORTED SIDE EFFECTS TO BUPRENORPHINE

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

Most are mild

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

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

TABLE 10: COMMON SIDE EFFECTS WITH OPIOID MAINTENANCE TREATMENT

Not all of these may occur with buprenorphine

Side effect	Common causes	Things that you can do
Feeling drowsy after taking dose	<ul style="list-style-type: none"> • Dose too high • Other drug use (legal or illegal) 	<p>Lower the maintenance dose and review other medications the patient may be taking</p> <p>Review use of sedative and other drugs affecting cognition</p>
Withdrawal symptoms maximal before next dose	<ul style="list-style-type: none"> • Dose too low • Changes in legal or illegal drugs that patient may be using. 	Raise maintenance dose or review other drugs patient is taking
Withdrawal precipitated by buprenorphine dose	<ul style="list-style-type: none"> • Occurs early in treatment (or after absence from treatment) when buprenorphine dose administered soon after opioid use (e.g. heroin, methadone, morphine) 	<p>Transient effect. Aim to prevent by patient education. Delay buprenorphine dose until patient experiencing opioid withdrawal</p> <p>Discourage use of on-top heroin.</p>
Headache	<ul style="list-style-type: none"> • Common in first week of buprenorphine treatment. • Other causes of headache 	Side effect is transient and generally mild. Consider aspirin or paracetamol. Consider other causes
Nausea	<ul style="list-style-type: none"> • Common early in treatment, particularly if buprenorphine dose too high. 	Side-effect usually transient (days). Avoid rapid dose increases. Consider dose-reduction if persistent
Constipation	<ul style="list-style-type: none"> • All opioids do this. Will be made worse by lack of dietary fibre, fluid intake or exercise 	Encourage fibre intake (fruit, cereals, vegetables), fluids, and regular exercise.
Weight gain, particularly for women	<ul style="list-style-type: none"> • Fluid retention caused by opioids — more likely on high doses • Eating more while in treatment; high salt intake 	<p>Lower dose</p> <p>Reduce fat and salt in diet, exercise regime</p>
Poor sleep	<ul style="list-style-type: none"> • Dose too low and causing withdrawal at night; or • Dose too late at night, causing stimulation at time of peak effects • Other drugs (particularly stimulants in the evening, such as coffee, nicotine, amphetamines) • General anxiety or irregular sleep pattern • Depressive illness 	<p>Review maintenance dose and review other medications</p> <p>Follow sleep hygiene recommendations.</p>

Side effect	Common causes	Things that you can do
Amenorrhoea or oligomenorrhoea	<ul style="list-style-type: none"> All opioids can do this May be related to lifestyle stressors, poor diet, and general poor health 	<p>Periods may return after cessation of heroin use, or following withdrawal from opioids.</p> <p>Address other causes</p>
Lowered sex drive	<ul style="list-style-type: none"> More common with a high dose Can be many other psychological factors (such as anxiety, poor relationship with partner etc...) 	Review dose
Dental problems	<ul style="list-style-type: none"> All opioids reduce saliva flow Poor diet, dental hygiene 	Encourage oral hygiene, dental floss and use of sugar free gum. Dental check-up. Reduce intake of sugary drinks and sweet food

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

5.2 Overdose

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

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

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

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

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

In the event of depression of respiratory or cardiac function:

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

5.3 Intoxicated presentations

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

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

5.4 Incorrect dose administered

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

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

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

5.5 Diversion of buprenorphine

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

Reasons cited by patients for diverting buprenorphine include:

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

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

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

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

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

5.6 Investigations

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

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

5.7 Analgesia requirements for patients on buprenorphine

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

Acute pain

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

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

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

Chronic Pain

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

5.8 Pregnancy and lactation

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

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

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

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

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

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

Substitution treatment during pregnancy

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

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

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

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

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

Withdrawal during pregnancy

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

The patient who becomes pregnant while on buprenorphine treatment

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

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

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

The pregnant heroin user not in treatment

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

Neonatal monitoring

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

Breast-feeding

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

