Opioid treatment of opioid addiction

SUMMARY

Opioid-related problems, including addiction, are increasing in Australia and more medical practitioners are likely to have contact with such patients. Addiction is a chronic disease, but opioid substitution treatment can reduce both mortality and morbidity.

There is a substantial evidence base for opioid substitution treatment. It is of benefit to individual patients and also, if adopted by a greater number of prescribers, to public health.

Opioid substitution is not suitable for all patients. It should also only be used as part of the patient’s rehabilitation.

The drugs which are used include methadone, naltrexone and buprenorphine with or without naloxone. Regular assessments are needed, not only to monitor for efficacy and safety, but also to retain the patient in the treatment program.

Introduction

Most medical practitioners will see patients who have become addicted to illegal drugs. In addition, with increasing opioid prescribing in Australia, more patients are developing prescribed opioid addiction.

Opioid addiction or dependence syndrome are synonymous terms which refer to a state of compulsive drug use despite related harm. This is exemplified by continued opioid injecting despite sustaining overdoses or infections. In other opioid dependent patients (for example with prescribed opioid dependence) excessive or unsanctioned use may be correlated with drug-related impairment (such as sedation or overdose) and accidents. Addiction can be considered as a chronic disease, with a relapsing and remitting pattern, significant long-term morbidity and an increased risk of death.2,3

One approach to managing addiction is the use of opioid substitution therapy with drugs such as methadone. This therapy has a substantial evidence base for improving physical and social health outcomes (reducing drug crimes, blood-borne viral spread and overall mortality).4-6

The provision of opioid substitution therapy is not simply maintaining addiction, because it also significantly reduces harm. It is therefore appropriate that methadone is included in the World Health Organization’s Essential Medicines List for treating opioid addiction.9

The decision to use opioid substitution therapy

Identifying addiction involves applying diagnostic criteria based on history, examination and urine drug testing.4-8 Australian states and territories maintain information about patients who have been notified as drug dependent and those who have previously received opioid substitution therapy. These details can be accessed via confidential communication with the local health department. When there is diagnostic uncertainty or case complexity, referral to a specialist in addiction medicine is recommended.

Not every patient with opioid addiction is suitable for opioid substitution therapy (Box 1). Consideration of alternative therapies is therefore necessary. These include abstinence-focused programs, behavioural interventions – particularly contingency management approaches10 – and self-directed interventions such as Narcotics Anonymous. If these strategies are unsuccessful or deemed inappropriate, opioid substitution therapy is considered.

Box 1 Assessing suitability for opioid substitution therapy

<table>
<thead>
<tr>
<th>Requirements</th>
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<tbody>
<tr>
<td>Addiction to opioids</td>
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<tr>
<td>Ongoing risk of opioid-related harms</td>
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<tr>
<td>Other treatment options ineffective or unsuitable</td>
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<td>Capacity for informed consent</td>
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<td>Circumstances appropriate (e.g. able to access pharmacy and take opioid substitution therapy)</td>
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<table>
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<th>Contraindications</th>
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<tr>
<td>Proven or likely sensitivity (or allergy) to some form of opioid substitution therapy</td>
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<tr>
<td>Pregnancy generally excludes treatment with buprenorphine with naloxone, and naltrexone</td>
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<tr>
<td>Active current alcohol dependence (e.g. daily drinking)</td>
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<tr>
<td>QTC prolongation syndrome with methadone – especially when combined with conditions or other drugs which prolong the QTC interval</td>
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<tr>
<td>Travel to some countries where opioid substitution therapy is not sanctioned</td>
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Key words
buprenorphine, methadone, naloxone, naltrexone, opioid substitution treatment

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There are two indications for opioid substitution therapy – brief treatment of opioid withdrawal and prolonged maintenance therapy. While the former is used in crisis intervention, only the latter has good correlation with long-term outcomes like remission and recovery.

**Management of withdrawal**

Short-term prescribing of an opioid substitute (such as buprenorphine) in reducing doses, supervised daily (or in an inpatient ‘detox unit’) for about a week, is used to manage acute opioid withdrawal symptoms (Table). Supervised dosing reduces the risk of intoxication, for example if the patient continues using other drugs. Later, the patient should be offered a general health review and relapse prevention counselling provided by local drug rehabilitation agencies. Importantly, the patient’s risk of overdose is increased following any prolonged period of abstinence (for example after hospitalisation, release from prison), therefore medical counselling about overdose prevention is essential.5,13

**Maintenance**

Opioid substitution therapy is mainly used for long-term drug rehabilitation, as in the methadone maintenance program. Such programs have proven efficacy, but have barriers including low numbers of prescribers5,6 and patient costs.

**Potential problems**

The risks of opioid substitution therapy include the drug’s potential for adverse effects.15 There is an increased risk of toxicity during methadone’s induction period, but there are guidelines to help minimise this problem.5 There is a risk of drug interactions especially if the patient continues using illicit drugs. Prescription drugs such as phenytoin, rifampicin and the HIV protease inhibitors also interact.16-18

The risk of diversion (that is, diverting take-away supplies to ‘other people’ for financial or other gain) needs to be appraised. This is especially important if the patient is living in a group household with other illicit drug users. Also consider if there are young children in the house (accidental exposure risk).

Some occupations, such as the airline and mining industries, do not permit any use of opioids. Opioid substitution therapy poses risks for driving, mostly during induction and dose adjustment. When combined with other sedating drugs (alcohol, benzodiazepines, antihistamines) this risk is increased. However, once a patient is on a stable, long-term dose and there are no signs suggesting opioid impairment (miosis with sedation, unsteady gait), they may be able to drive.19,20

Opioid substitution therapy in special circumstances (for example in inpatients, pain management and pregnancy) and travel, particularly overseas, poses problems for patients.5,21

**Choice of therapy**

All forms of opioid substitution therapy are more effective when used as part of a comprehensive approach to drug rehabilitation (Box 2). Opioid substitution therapy includes methadone (a full agonist), buprenorphine (a partial agonist) and naltrexone (antagonists). All have different formulations and Pharmaceutical Benefits Scheme (PBS) indications.

**Methadone**

Methadone syrup 5 mg/mL is available with or without added ethanol and sorbitol (some patients have preferences). It is a full agonist at the mu opioid receptor which is possibly why it is preferred by many patients. The syrup formulation is useful for dispensing under direct supervision, because liquid cannot be concealed under the tongue like tablets. Methadone is approved for use in pregnancy. Its metabolism does not produce active metabolites so it can be cautiously used in patients with liver or renal impairment.

Methadone has slightly more drug interaction risks than buprenorphine. Many patients taking methadone also smoke and there is the potential for toxicity if they suddenly stop smoking. There is a risk of QTc prolongation at higher doses (for example more than 100 mg daily) and in those with other risk factors for QTc prolongation.22,23

Methadone in its oral formulation has approximately 70% bioavailability compared with the parenteral

<table>
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<tr>
<th>Drug</th>
<th>Dose</th>
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<tr>
<td>Buprenorphine*</td>
<td>Start at 4 mg (test dose) then up to a total of 8 mg on day one, thereafter reduce by 2 mg daily</td>
</tr>
<tr>
<td>Methadone syrup*</td>
<td>Start at 25 mg on day one, thereafter reduce by 2-5 mg daily</td>
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<tr>
<td>Metoclopramide</td>
<td>10 mg tablets (or intramuscularly if inpatient or in clinic) 6-hourly as needed for about three days</td>
</tr>
<tr>
<td>Loperamide</td>
<td>2 mg tablets for problematic diarrhoea in opioid withdrawal, as needed for about three days</td>
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Benzodiazepines are generally avoided when specific symptomatic care with opioid substitution therapy is provided.

Although an off-label use, clonidine is sometimes used to treat acute opioid withdrawal in situations where avoiding opioids is preferred.

While not specific to opioid withdrawal treatment, metoclopramide and loperamide are commonly used in providing symptom relief

* begin after opioid withdrawal signs appear
and therefore the combination formulation is not approved for use by pregnant women or those contemplating pregnancy. Evidence supporting the safety of buprenorphine alone is emerging. It may possibly be associated with less neonatal abstinence syndrome than methadone. Buprenorphine alone is usually only recommended with informed consent in pregnancy or when naloxone allergy exists. In the vast majority of instances, the combination formulation is preferred.

### Naltrexone

Naltrexone is listed on the PBS only for alcohol dependence, however it has been used for opioid addiction as it may facilitate the maintenance of opioid abstinence. While naltrexone has efficacy in treating alcohol dependence, the evidence for naltrexone’s efficacy in treating opioid addiction is less impressive. Naltrexone is not recommended for facilitating rapid opioid detoxification. As it is not listed on the PBS, naltrexone costs patients up to approximately $180 per month.

Naltrexone is formulated as a 50 mg tablet. Implant formulations are available, but these are not approved by the Therapeutic Goods Administration, and the National Health and Medical Research Council (along with some medical defence insurers) has issued cautions regarding the lack of safety and efficacy data. In the USA, a depot naltrexone formulation is available for the treatment of alcohol dependence and can be used for treating opioid addiction.

A minority of patients seek this ‘antagonist’ treatment, but if naltrexone is used, it is recommended to be prescribed with an adherence strategy that involves the patient’s spouse or other reminders. Opioid substitution therapy with an agonist has primary (rewarding) and secondary (avoidance of withdrawal) reinforcing efficacy and so patients are more likely to remember to take their treatment.

### Considering dose and duration of therapy

The starting dose is always low (for example methadone 20 mg, buprenorphine 4 mg, naltrexone 25 mg). Apart from methadone the dose is mostly increased to the effective maintenance dose within days. To reduce the risk of toxicity, not increasing the methadone dose more than 10 mg per week during induction (later, 10–20 mg per week) is recommended and no take-away doses are approved. As methadone has a long half-life, accumulation will occur slowly and steady-state concentrations are not achieved for, on average, 5–7 days. The efficacy of any increased dose of methadone is therefore evaluated after a week. Treatment is titrated to effect which can be assessed by reduced use of other opioids.
(for example illicit heroin injecting) and reduction of withdrawal and craving symptoms. An average target dose range of 60–80 mg methadone or approximately 16 mg buprenorphine daily has been correlated with better outcomes.4,22 Take-away doses of opioid substitution therapy are only approved when the prescriber is satisfied that the patient is stable and the risk for diversion is reduced.5 Divided daily doses of methadone (and buprenorphine) are sometimes used for inpatients with acute pain (analgesic efficacy being of shorter duration than other opioid effects),21,24 or in situations of enhanced metabolism (for example pregnancy and interactions with enzyme-inducing drugs such as rifampicin) to avoid very high peak concentrations and extend the duration of effects.

Addiction is a chronic disease so prolonged treatment (for example more than a year) has the best outcomes, but many patients will want to discontinue opioid substitution therapy after relatively brief periods of improvement. Retaining a patient in therapy is therefore an ongoing challenge for the prescriber. While many Australian opioid substitution programs retain patients for less than 12 months, treatment outcomes are better when longer retention is achieved. Measuring treatment retention rates provides a good method of evaluating opioid substitution therapy programs.4,22,28

**Evaluating safety and efficacy**

Monitoring opioid substitution therapy is part of the management plan. This includes regular assessment for any adverse events and the patient’s progress.

There are many long-term problems and other complications of opioid therapy including gut motility disturbances, hypogonadism, hyperalgesia, osteoporosis, tooth decay, hyperhidrosis, sleep disorder and driving hazards.15-20 Monitoring safety includes ensuring safe storage and transport of the medicine by the patient. Buprenorphine film may melt in temperatures above 25°C. Using a lockable box to store take-away doses is essential when children are at home.

As patients see their pharmacist frequently, the pharmacist can give the prescriber further information about the patient’s treatment adherence and daily functioning. Because addiction is associated with significant mental and physical risks and adversely impacts on families, opioid substitution therapy is recommended to be provided in a family inclusive context. This also helps the prescriber obtain further important information about the patient’s functioning. In most states, prescribers and pharmacists need accreditation to provide opioid substitution therapy and there is some state variability in regulations, hence familiarity with state guidelines is necessary. National treatment guidelines are in press1 and Box 3 summarises recommended monitoring.

**Access to treatment**

Opioid substitution therapy was originally restricted to accredited prescribers, however recently a number of states have allowed any medical practitioner to prescribe the buprenorphine with naloxone formulation. During any temporary absence of an accredited prescriber (for example in a group practice), state regulations generally permit another prescriber from the same practice, who has access to the treatment plan, to cover the continuation of a regular prescription for opioid substitution therapy. Unfortunately, many doctors who undertake accreditation for opioid substitution therapy do not prescribe for various reasons. If more general practitioners prescribed opioid substitution therapy, additional general healthcare advantages would be likely, for example disease screening, immunisation, contraception and more comprehensive care.

The low number of prescribers diminishes public access to this essential treatment and is a public health problem.14 There are also concerns about prescribing other opioids to patients undergoing opioid substitution therapy because of the risk of toxicity and breaching the sanctions of the patient’s rehabilitation program.10

Although methadone and buprenorphine formulated for opioid substitution therapy are fully funded under the PBS, the pharmacist-supervised daily dispensing...
requirement is not. That costs, on average, $6 per day, which is not insignificant for many patients. Some hospital pharmacies or public-funded clinics may, for a time, waive the dispensing fee. As resources are limited, usually such access to free treatment is restricted to special cases.

Conclusion

Opioid substitution therapy is a highly effective component of comprehensive drug rehabilitation for opioid addiction. It reduces mortality and morbidity. All states and territories provide services to support opioid substitution therapy, including detailed treatment guidelines. However, the numbers of patients seeking treatment are increasing, while the numbers of prescribers are decreasing.

Different opioid substitution therapy formulations allow treatment selections better suited to the individual patient.

It is important to try and keep the patient in therapy. Regular follow-up is advised to monitor the patient’s progress.

Dr McDonough was a medical adviser to Reckitt-Benckiser regarding buprenorphine until 2011.

REFERENCES