ARTICLE

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,[1] 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).[4-8]

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 approaches[10] – 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**

Requirements

Addiction to opioids

Ongoing risk of opioid-related harms

Other treatment options ineffective or unsuitable

Capacity for informed consent

Circumstances appropriate (e.g. able to access pharmacy and take opioid substitution therapy)

Contraindications

Proven or likely sensitivity (or allergy) to some form of opioid substitution therapy

Pregnancy generally excludes treatment with buprenorphine with naloxone, and naltrexone

Active current alcohol dependence (e.g. daily drinking)

QTc prolongation syndrome with methadone – especially when combined with conditions or other drugs which prolong the QTc interval

Travel to some countries where opioid substitution therapy is not sanctioned

Michael McDonough
Director
Department of Addiction Medicine and Toxicology
Western Hospital
Melbourne

Key words
buprenorphine, methadone, naloxone, naltrexone, opioid substitution treatment

Aust Prescr 2013;36:83–7

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.[11-13]

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 prescribers[14] 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 naloxone 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 **Options for managing acute opioid withdrawal**

Drug	Dose
Buprenorphine*	Start at 4 mg (test dose) then up to a total of 8 mg on day one, thereafter reduce by 2 mg daily
Methadone syrup*	Start at 25 mg on day one, thereafter reduce by 2–5 mg daily
Metoclopramide	10 mg tablets (or intramuscularly if inpatient or in clinic) 6-hourly as needed for about three days
Loperamide	2 mg tablets for problematic diarrhoea in opioid withdrawal, as needed for about three days

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

Box 2 **Elements of comprehensive drug rehabilitation**

Targeted counselling and education regarding blood-borne viruses, injecting and overdose

Primary health care including contraception, viral screening, vaccination – consider hepatitis B, tetanus and pneumococcal vaccines

Assessment and management of any concurrent substance use like benzodiazepines, smoking

Assessment and management (and/or shared care) of any concurrent comorbidities (e.g. hepatitis C related liver disease, diabetes, chronic obstructive pulmonary disease, dental disease)

Assessment and management of concurrent mental health problems (e.g. depression, anxiety)

Psychosocial support including assistance with family, housing, legal, work and other related problems

Relapse prevention counselling – cognitive behavioural therapy

formulation. When 'nil orally' restrictions apply a 30% (of usual) dose reduction is recommended. Patients on methadone who have acute pain will usually require higher than usual doses of opioid analgesics (because of tolerance) while having their regular daily methadone dose maintained.[21,24]

Buprenorphine and naloxone

Buprenorphine is formulated alone or in combination with naloxone. In the combination the buprenorphine to naloxone ratio is 4:1, for example 8 mg buprenorphine with 2 mg naloxone. In addition to sublingual tablets, the combination is formulated as a film that dissolves rapidly under the tongue. In comparison with methadone, buprenorphine is a partial agonist and antagonist at the mu opioid receptor so it is often recommended as first line in cases where the degree of opioid tolerance is lower (as estimated by considering daily dose, potency, route of administration and the observed severity of opioid withdrawal).

The combination of naloxone with buprenorphine generally reduces the risk of diversion or self-injection, because the predominant effect following intravenous use is naloxone-induced withdrawal (aversive). There are comparatively few deaths associated with buprenorphine opioid substitution therapy in contrast with methadone.[25] The combination has therefore been approved in some states for prescription by any medical practitioner, with some caseload limitations.

Naloxone has not been proven safe in pregnancy 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.[26] 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,[27] the evidence for naltrexone's efficacy in treating opioid addiction is less impressive.[5,8] Naltrexone is not recommended for facilitating rapid opioid detoxification.[4] As it is not listed on the PBS, naltrexone costs patients up to approximately $180 per month.[5,8]

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.[5,8]

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.[4-7,28] 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.[4-7,28,29]

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.

Box 3 **Monitoring the efficacy and safety of opioid substitution therapy**

- Pay particular attention to methadone dose during induction – first two weeks (e.g. methadone 20 mg to 40 mg maximum)
- Regular review of treatment progress and any new drug therapy – assess risk of interaction or diversion
- Engage family or significant others in treatment monitoring (e.g. occasional family inclusive consultations)
- Educate family or significant others in drug risk management (e.g. recognising possible toxicity)
- Regular communication with the pharmacist who frequently sees the patient
- Regular physical examination includes looking for any injection sites and any signs of drug-related impairment (e.g. is patient fit to drive?). Always document these findings.
- Random urine drug screening
- Consider use of breathalyser and selected blood tests where appropriate (e.g. gamma-glutamyl transferase)
- Careful consideration of risk before approving any take-away, unsupervised, doses
- Compliance with treatment guidelines

There are many long-term problems and other complications of opioid therapy including gut motility disturbances, hypogonadism, hyperalgesia, osteoporosis, tooth decay, hyperhydrosis, 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 press[5] 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.[30]

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.

Q:

SELF-TEST QUESTIONS

True or false?

3. The effect of a change in the dose of methadone cannot be evaluated for 5–7 days.

4. Methadone is contraindicated in pregnancy.

Answers on page 107

REFERENCES

1. Leong M, Murnion B, Haber PS. Examination of opioid prescribing in Australia from 1992 to 2007. Intern Med J 2009;39:676-81.
2. McLellan AT, Lewis DC, O'Brien CP, Kleber HD. Drug dependence, a chronic medical illness: implications for treatment, insurance, and outcomes evaluation. JAMA 2000;284:1689-95.
3. Saitz R, Larson MJ, Labelle C, Richardson J, Samet JH. The case for chronic disease management for addiction. J Addict Med 2008;2:55-65.
4. Mattick RP, Ward J, Hall W. Methadone maintenance treatment and other opioid replacement therapies. Amsterdam: Harwood Academic Publishers; 1998.
5. Gowing L, Ali R, Dunlop A, et al. National policy and guidelines for the pharmacological treatment of opioid dependence. Commonwealth of Australia. In press 2013.
6. Mattick RP, Breen C, Kimber J, Davoli M. Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. Cochrane Database Syst Rev 2003;2:CD002209.
7. Mattick RP, Kimber J, Breen C, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. Cochrane Database Syst Rev 2008;2:CD002207.
8. Minozzi S, Amato L, Vecchi S, Davoli M, Kirchmayer U, Verster A. Oral naltrexone maintenance treatment for opioid dependence. Cochrane Database Syst Rev 2011;4:CD001333.
9. WHO Essential Medicines List. 17th ed. 2011. www.who.int/selection_medicines/list/en/index.html [cited 2013 May 3]
10. Stitzer M, Petry N. Contingency management for treatment of substance abuse. Annu Rev Clin Psychol 2006;2:411-34.
11. Bell J, Zador D. A risk-benefit analysis of methadone maintenance treatment. Drug Saf 2000;22:179-90.
12. Fugelstad A, Stenbacka M, Leifman A, Nylander M, Thiblin I. Methadone maintenance treatment: the balance between life-saving treatment and fatal poisonings. Addiction 2007;102:406-12.
13. Clausen T, Anchersen K, Waal H. Mortality prior to, during and after opioid maintenance treatment (OMT): a national prospective cross-registry study. Drug Alcohol Depend 2008;94:151-7.
14. Longman C, Lintzeris N, Temple-Smith M, Gilchrist G. Methadone and buprenorphine prescribing patterns of Victorian general practitioners: their first 5 years after authorisation. Drug Alcohol Rev 2011;30:355-9.
15. Benyamin R, Trescot AM, Datta S, Buenaventura R, Adlaka R, Sehgal N, et al. Opioid complications and side effects. Pain Physician 2008;11:S105-20.
16. Weschules DJ, Bain KT, Richeimer S. Actual and potential drug interactions associated with methadone. Pain Med 2008;9:315-44.
17. Lintzeris N, Nielsen S. Benzodiazepines, methadone and buprenorphine: interactions and clinical management. Am J Addict 2010;19:59-72.
18. Wang D, Teichtahl H. Opioids, sleep architecture and sleep-disordered breathing. Sleep Med Rev 2007;11:35-46.
19. Lenne MG, Dietze P, Rumbold GR, Redman JR, Triggs TJ. The effects of the opioid pharmacotherapies methadone, LAAM and buprenorphine, alone and in combination with alcohol, on simulated driving. Drug Alcohol Depend 2003;72:271-8.
20. Bramness JG, Skurtveit S, Morland J, Engeland A. An increased risk of motor vehicle accidents after prescription of methadone. Addiction 2012;107:967-72.
21. Murnion B. Management of opioid substitution therapy during medical intervention. Intern Med J 2012;42:242-6.
22. Mayet S, Gossop M, Lintzeris N, Markides V, Strang J. Methadone maintenance, QTc and torsade de pointes: who needs an electrocardiogram and what is the prevalence of QTc prolongation? Drug Alcohol Rev 2011;30:388-96.
23. Roy AK, McCarthy C, Kiernan G, McGorrian C, Keenan E, Mahon NG, et al. Increased incidence of QT interval prolongation in a population receiving lower doses of methadone maintenance therapy. Addiction 2012;107:1132-9.
24. Alford DP, Compton P, Samet JH. Acute pain management for patients receiving maintenance methadone or buprenorphine therapy. Ann Intern Med 2006;144:127-34.
25. Bell J, Trinh L, Butler B, Randall D, Rubin G. Comparing retention in treatment and mortality in people after initial entry to methadone and buprenorphine treatment. Addiction 2009;104:1193-200.
26. Jones HE, Kaltenbach K, Heil SH, Stine SM, Coyle MG, Arria AM, et al. Neonatal abstinence syndrome after methadone or buprenorphine exposure. N Engl J Med 2010;363:2320-31.
27. Rosner S, Hackl-Herrwerth A, Leucht S, Vecchi S, Srisurapanont M, Soyka M. Opioid antagonists for alcohol dependence. Cochrane Database Syst Rev 2010;CD001867.
28. Ridge G, Gossop M, Lintzeris N, Witton J, Strang J. Factors associated with the prescribing of buprenorphine or methadone for treatment of opiate dependence. J Subst Abuse Treat 2009;37:95-100.
29. Winstock AR, Lintzeris N, Lea T. "Should I stay or should I go?" Coming off methadone and buprenorphine treatment. Int J Drug Policy 2011;22:77-81.
30. Kurdyak P, Gomes T, Yao Z, Mamdani MM, Hellings C, Fischer B, et al. Use of other opioids during methadone therapy: a population-based study. Addiction 2012;107:776-80.