ARTICLE

Safe prescribing of opioids for persistent non-cancer pain

Michael McDonough
Director
Addiction Medicine and Toxicology
Western Hospital
Melbourne

Key words
adverse effects, opiates, substance use disorder

Aust Prescr 2012;35:20–4

SUMMARY

A judicious approach in considering opioid therapy and choosing an appropriate opioid is needed.

After an initial opioid trial, therapy should only be continued when there is reasonable evidence that it is effective and safe.

The evidence for harm associated with long-term opioid prescribing is mounting while there is little evidence to support long-term efficacy. In many cases, reducing and eventually stopping opioid therapy may be the best course of action.

Commitment by both the prescriber and the patient to a treatment plan which includes regular reviews is essential if opioid therapy is prolonged.

Introduction

The prevalence of opioid prescribing in Australia, particularly for persistent non-malignant pain, has been steadily increasing.[1] There is emerging evidence of a corresponding increase in deaths where opioids were detected.[2] Similar trends have been reported in the USA with an alarming escalation in opioid-related deaths.[3] Safe opioid prescribing is best defined by the principles for the quality use of medicines in Australia's National Medicines Policy.[4] This recommends that any reason to prescribe needs to be considered judiciously,[5] then appraised for appropriateness, and thereafter monitored for safety and efficacy.

State legislation

To prescribe opioids beyond eight weeks, most states and territories require the prescriber to have a state permit. However in NSW, a permit is only needed for prescribing opioids to patients with drug dependence. All other jurisdictions need to be notified for any patient who is drug dependent.

Considering opioid treatment

There is little evidence for the efficacy of long-term opioid use in persistent non-malignant pain and in trials (up to three months) many patients experienced adverse drug effects.[6] However, there is expert consensus that opioid analgesics be considered when other treatments have been inadequate.

Before undertaking a longer-term period of opioid treatment, the patient should be assessed following an initial trial period, for example a month (see Box). After that, the prescriber should identify evidence of improved patient function correlated with opioid use. It is imperative that the patient give informed consent at the start of the trial, acknowledging the possibility of a negative outcome and withdrawal of therapy.

The definition of pain[7] as 'an unpleasant sensory and emotional state' reminds us that a significant proportion of a patient's suffering will be related to the emotional contribution to their pain perception. Some patients may report that all treatments have failed including physical and psychological therapy, however this may represent the patient's resistance to engage in appropriate treatment and not necessarily a 'failure of all therapies'. Indeed, physical and psychological interventions may vary in their effect and appropriateness for individual patients, just as drug therapies do.

Chronic pain and depression often coexist and depression may be a reason why some patients respond poorly to initial treatments. If a patient is not responding to opioids, other pain management strategies may need to be considered including referral for an assessment at a specialist pain clinic.

Previous or current substance use disorder increases the risk for addiction and related problems. Screening tools may help to identify this.[8] Inadequate compliance with previous therapy, extreme frustration with pain symptoms, inappropriate pursuit of a 'cure', requests based on the second-hand experience of other patients and the patient who predominantly conceptualises pain management as taking medication (chemical coping) would all be reasons for increased caution. The Royal Australasian College of Physicians Prescription Opioid Policy (2009) is freely available to download from www.racp.edu.au.[9] It provides an excellent review and guidelines for managing chronic non-malignant pain.

Relative contraindications

There are numerous contraindications to opioid use. The risk of developing opioid dependence during long-term opioid analgesic prescribing in some patients is significantly increased, for example in

those with a history of substance use disorder. To avoid iatrogenic dependence, consult with a pain or addiction medicine specialist when a patient develops 'tolerance' and is seeking a dose increase, particularly when any problematic opioid-related behaviours appear.

Other factors that need to be considered when assessing the patient include the following:

- previous poorly tolerated opioid treatment
- drugs with potential interactions, e.g. tramadol with other serotonergic drugs such as selective serotonin reuptake inhibitors can cause serotonin toxicity
- psychiatric risk – previous intentional overdoses
- depression
- dementia
- obstructive sleep apnoea
- severe gastro-oesophageal reflux disease or gastrointestinal hypomotility
- organ failure, e.g. renal impairment may result in morphine accumulation
- other existing conditions, e.g. many patients with porphyria have sensitivity to several opioids
- occupations, e.g. patients working in the aviation or mining industry and other situations that impose **zero tolerance** for any drugs of dependence.

Choosing an appropriate opioid

An appropriate opioid best avoids the risk of drug interactions, disease interactions and patient 'interactions' (for example patients may favour 'tamper-resistant' options if children are at home).

Oral long-acting opioids are recommended because short-acting opioids wear off quickly (particularly given tolerance over time), require frequent repeat dosing and, if used chronically, may cause 'analgesic rebound' or break-through pain. Long-acting transdermal and sublingual opioid formulations might be considered for patients who have problems with swallowing tablets.

Patients with drug dependence strongly prefer short-acting drugs with faster onset of action and with higher peak blood levels (that is, quick reward). They will often state a preference for immediate-release preparations or resist taking long-acting drugs.

The chronic use of injectable drugs is inappropriate for persistent pain because recurrent injections lead to tissue injury (which reduces drug absorption), carry the risk of infection as a consequence of chronic injecting and have a greater risk for addiction and diversion*. People who are drug dependent typically manifest a very strong preference for their drug of choice and such patients can be remarkably convincing in their efforts to persuade a compassionate doctor that such therapy is the only effective treatment. Pethidine is now generally viewed as a poor opioid analgesic in comparison with most others now available and is inappropriate for persistent pain.[10]

Patient reports of 'drug allergy' might instead be dose-related adverse effects like nausea or pruritis and therefore dose reduction is suggested rather than avoidance, or referral to clinical immunology for specific drug sensitivity testing. Sometimes the latter may be necessary if options are restricted by the patient reporting 'allergy' to multiple opioids particularly if there is strong patient preference for treatment with a specific drug, for example pethidine.

Evaluating the efficacy of ongoing opioid therapy

After a successful initial therapeutic trial, continuing opioid treatment requires commitment to a treatment plan of regular reviews of efficacy and safety. A common problem faced by some doctors who

Box **Trialling opioids in patients with non-malignant pain**

Assess the potential merits and contraindications for opioids in patients unresponsive to other 'first-line' treatments
Consider whether depression is a complication and needs treatment before proceeding with a trial of opioids
Formulate a treatment plan for the next month which the patient agrees to. Include weekly reviews and explain the possibility that treatment may not prove helpful and may need to be discontinued. Have the patient fill in a Brief Pain Inventory.
Start treatment with a long-acting opioid of moderate efficacy
Recommend the patient keep a daily diary to monitor activities and pain-related impairment
Ensure the opioids will be safely stored in the home and secure from children
Establish a dialogue with the pharmacist
Review the patient weekly with a family member and the patient's diary. Appraise treatment efficacy with a Brief Pain Inventory and witness accounts (family members, pharmacist). If the patient has a poor response, consider a dose change. If they are unable to tolerate treatment, consider switching to an alternative opioid starting at a low dose.
Monitor for adverse effects (e.g. developing constipation, sleep problems, drowsiness, miosis, slurred speech)
Recommend the patient avoids driving until further assessment of their opioid therapy. Consider baseline Epworth Sleepiness Scale (ESS) to assess possible daytime somnolence. Ask the spouse about any current snoring or sleep problems (opioids may increase these conditions when taken at night).

* Diversion of a drug means that it has been given or sold to, or taken by, a person for whom it was not prescribed

have been formally investigated for their opioid prescribing has been an apparent deficient or absent opioid treatment plan. Just as treating hypertension requires periodic measurements of blood pressure, continuing opioid therapy requires documentation of ongoing monitoring of patient function. A pain management form[11] for patients can be used as a written management plan. Sustained improvement that can be correlated with opioid therapy, without unacceptable adverse effects, constitutes reasonable justification to continue therapy. Correlating opioid therapy with functional improvement is more important than reduction of patient-perceived pain. Relying on a patient's own opinion of their improvement is subjective. Better evidence includes examination of the patient's functioning during regular clinic attendance, reports from their pharmacist and family together with the patient's self-report and use of validated questionnaires such as the Brief Pain Inventory.[12]

Correlating opioid therapy with functional improvement is more important than reduction of patient-perceived pain

If prescribing beyond 12 months, a second opinion from a specialist (for example in pain medicine) is required to fulfil Pharmaceutical Benefits Scheme Authority indications.

Adherence

It is also important to assess the patient's adherence to treatment by reports from reliable informants. Occasional urine drug screening may be useful. If a patient reports benefit from an opioid and yet one or more urine drug screens show it is not present, diversion should be suspected. There is evidence that even some cancer patients taking opioids have diverted these drugs.[13] The practice of medication swapping, borrowing and sharing also needs to be considered as these are not uncommon behaviours.[14] Collaboration with the patient's community pharmacist is also a helpful way of improving adherence.

Monitoring the safety of opioids

Opioids are not just analgesics, they have a range of effects including endocrine, immunological, cognitive and emotive. Long-term opioid use is associated with numerous adverse reactions (listed in Table 1).[15] The continuing management plan needs to incorporate a process of regular review for the risk and occurrence of adverse drug events. This includes monitoring the patient physically, mentally and in regard to areas of important functioning, for example the ability to drive, work, participate in hobbies, and for possible aberrant drug-related behaviours.[8]

Opioid dosages over 120 mg (mg morphine equivalent) correlate with an increased risk of mortality.[16] The comparative safety of opioids compared to other drugs (for example non-steroidal anti-inflammatory drugs) in older adults is questionable[17] and prescribing high-dose opioids long term carries greater risk for misuse.[18] While chronic pain of itself does not kill, prescribing opioids particularly in high doses and in conjunction with other sedatives like benzodiazepines does increase the mortality risk.[2,3,16,18]

Table 1 presents strategies for managing potential opioid-related adverse effects. Perceived risks (noting an absence of adverse opioid effects) and how they are addressed and managed should be documented in the treatment plan during regular clinical reviews.

Stopping opioids

When longer-term opioid treatment goals have not been met, treatment should be discontinued. This process is facilitated by having a pre-arranged treatment plan with the patient. Explain the need to stop opioids and set a reasonable timeline for gradual reduction of the dose (for example 10–20 mg morphine equivalent per week). Review the patient weekly and ensure they receive additional support during this time (for example supportive therapies like massage, hydrotherapy and counselling) and monitor the patient's mental state, as some people can experience mood disturbance during opioid withdrawal. In some cases, advice from a pain and/or addiction medicine specialist may be warranted. Temporary 'setbacks' may occur but should be contained and the goal of completing opioid withdrawal should be maintained.

Conclusion

Opioids are not universal painkillers but may have a role in managing persistent non-malignant pain for appropriately selected patients. Once commenced, ongoing evaluation of safety (adverse opioid events) and efficacy (with documentation) should guide clinical management. A treatment plan that incorporates the possibility of, and process for, stopping opioids is essential. For many patients, long-term opioid use may not prove safe and effective. ◁

Dr McDonough occasionally acts as a medical adviser to Reckitt-Benckiser regarding the use of buprenorphine in opioid addiction treatment.

Q:

SELF-TEST QUESTIONS

True or false?

3. Tramadol should be avoided in patients taking selective serotonin reuptake inhibitors.

4. Opioid doses above 200 mg are associated with an increased risk of death.

Answers on page 35

Table 1 **Managing opioid-induced adverse effects** [15]

ADVERSE EFFECT	SUGGESTED STRATEGY
Gastrointestinal	
Nausea and vomiting	Reduce dose, consider alternate formulation (sublingual, transdermal), exclude chronic constipation
Chronic constipation and related sequelae including abdominal pain, reflux, haemorrhoids, colonic hypomotility	Recommend regular bulking agent, extra fluids, non-osmotic laxatives
Reduced salivary flow posing dental problems	Six-monthly dentist reviews, brushing and flossing teeth, extra fluoride treatment, encourage salivary flow after meals, diet
Gastro-oesophageal reflux disease	Specific treatment e.g. proton pump inhibitor such as omeprazole
	Consider reducing or stopping opioids
Neurological	
Impaired cognition	Periodic assessment, mini-mental state examination
Impaired coordination	Heel-toe gait testing
Sedation	Consider monitoring with Epworth Sleepiness Scale (for excessive daytime somnolence) and with family and other witness accounts (e.g. pharmacist)
	Consider possibility of drug interaction (e.g. benzodiazepines) and review dosages and need
Hyperalgesia	Periodic assessment, avoid doses >120 mg (mg morphine equivalent)
Endocrine	
Hyperprolactinaemia (and galactorrhea)	Monitor prolactin
Hypogonadism	Monitor testosterone
Osteoporosis	Monitor from baseline, check vitamin D status, seek specialist guidance
Respiratory	
Exacerbation of obstructive sleep apnoea	Consult respiratory physician
Inducing central sleep apnoea	Likely contraindication (e.g. methadone), reduce dose, sleep study (polysomnography), consult respiratory physician
Respiratory depression	Especially in patients with type 2 respiratory failure (CO_2 retention) and those on home oxygen therapy
	Deterioration requires specialist intervention and probable opioid discontinuation
Cardiovascular	
Prolonged QTc	Electrocardiogram (particularly with methadone and oxycodone)
Psychiatric	
Mood disorder	Monitor from baseline, reduce dose and review
Addiction	Consult addiction specialist, consider referral to methadone program
Overdosage	Prescribe small amounts (e.g. weekly supply), ensure only one prescriber and likewise pharmacist, assess patient for depression
Other	
Fluid retention and oedema	Document, reduce dose, restrict sodium, consider a diuretic
Occupational and driving impairment	Establish baseline and review with reference to reliable co-informants
Diversion potential	Consider 'tamper-resistant' preparations, require patient to have secure storage (e.g. locked metal box), designate one pharmacy, note on script, fax script in advance
	Prescribers can also check with the Prescription Shopping Information Service (www.medicareaustralia.gov.au/provider/pbs/prescription-shopping/index.jsp#N10058)

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. Rintoul AC, Dobbin MD, Drummer OH, Ozanne-Smith J. Increasing deaths involving oxycodone, Victoria, Australia, 2000-2009. Inj Prev 2011;17:254-9.
3. Bohnert AS, Valenstein M, Bair MJ, Ganoczy D, McCarthy JF, Ilgen MA, Blow FC. Association between opioid prescribing patterns and opioid overdose-related deaths. JAMA 2011;305:1315-21.
4. National Medicines Policy. Quality Use of Medicines. Department of Health and Ageing. 1999. www.health.gov.au/internet/main/publishing.nsf/Content/nmp-quality.htm [cited 2012 Jan 6]

5. Wodak A, Cohen ML. The judicious use of opioids in managing chronic noncancer pain. Med Today 2010;11:10-8.
6. Furlan AD, Sandoval JA, Mailis-Gagnon A, Tunks E. Opioids for chronic noncancer pain: a meta-analysis of effectiveness and side effects. CMAJ 2006;174:1589-94.
7. International Association for the Study of Pain [IASP]. Definition of pain. www.iasp-pain.org/AM/Template.cfm?Section=Pain_Defi...isplay.cfm&ContentID=1728 [cited 2012 Jan 6]
8. Chou R, Fanciullo GJ, Fine PG, Adler JA, Ballantyne JC, Davies P, et al. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. J Pain 2009;10:113-30.
9. Prescription Opioid Policy: Improving management of chronic non-malignant pain and prevention of problems associated with prescription opioid use. Sydney 2009. www.racp.edu.au/index.cfm?objectid=D7FAA946-ACEE-2637-428D447EE5E581C3 [cited 2012 Jan 6]
10. Molloy A. Does pethidine still have a place in therapy? Aust Prescr 2002;25:12-3.
11. National Prescribing Service. My Pain Management Plan. 2010. www.nps.org.au/__data/assets/pdf_file/0005/88340/My_pain_plan.pdf [cited 2012 Jan 6]
12. Tan G, Jensen MP, Thornby JI, Shanti BF. Validation of the Brief Pain Inventory for chronic nonmalignant pain. J Pain 2004;5:133-7.
13. Inciardi JA, Surratt HL, Cicero TJ, Beard RA. Prescription opioid abuse and diversion in an urban community: the results of an ultrarapid assessment. Pain Med 2009;10:537-48.
14. Ellis J, Mullan J. Prescription medication borrowing and sharing: risk factors and management. Aust Fam Physician 2009;38:816-9.
15. Kalso E, Edwards JE, Moore RA, McQuay HJ. Opioids in chronic non-cancer pain: systematic review of efficacy and safety. Pain 2004;112:372-80.
16. Gomes T, Mamdani MM, Dhalla IA, Paterson JM, Juurlink DN. Opioid dose and drug-related mortality in patients with nonmalignant pain. Arch Intern Med 2011;171:686-91.
17. Solomon DH, Rassen JA, Glynn RJ, Lee J, Levin R, Schneeweiss S. The comparative safety of analgesics in older adults with arthritis. Arch Intern Med 2010;170:1968-78.
18. Sullivan MD, Edlund MJ, Fan MY, Devries A, Brennan Braden J, Martin BC. Risks for possible and probable opioid misuse among recipients of chronic opioid therapy in commercial and medicaid insurance plans: The TROUP Study. Pain 2010;150:332-9.

FURTHER READING

Bird S. Prescribing Schedule 8 drugs. Aust Fam Physician 2006;35:59-60.

Book review

Introduction to pharmaceutical calculations. 3rd ed.

Louis Roller
Honorary associate professor
Faculty of Pharmacy and Pharmaceutical sciences
Monash University
Melbourne

Rees JA, Smith I, Smith B.

London: Pharmaceutical Press; 2011. 245 pages.

Price: $76, members of the Pharmaceutical Society of Australia $59

The third edition of this British book, written by pharmacy educators, is an introduction to drug dosage and other pharmaceutical calculations. Each chapter contains learning objectives, numerous worked examples, sample questions and answers. It also includes new chapters on accuracy of measurement and updated worked examples.

However, I have reservations about its usefulness for Australian pharmacy students. I can envisage Australian pharmacy students, who come with high levels of mathematics skills, becoming quite annoyed at the rather simplistic content.

Most pharmacy schools have pharmaceutical calculations taught and assessed over the four years of the course and there are further assessments by the Pharmacy Board of Australia as part of pharmacists' registration examinations during their internship year.

This book also suffers from significant omissions, such as pharmacokinetic and clinical calculations that are relevant to modern-day pharmacy practice. Many of the examples are antiquated and the use of chloroform water (which appears in many examples) is banned in Australia. Again, in the Australian context, devoting a chapter on converting degrees Fahrenheit to Celsius and vice versa is probably irrelevant.

I cannot recommend this book as a text for pharmacy students in Australia.