The six Rs of managing high-risk opioid prescribing

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Background
High-dose opioid prescribing is associated with an increased risk of harms, including death.

Objective
The aim of this article is to discuss the concept of high-risk opioid prescribing, as well as relevant management strategies for patients on >100 mg oral morphine equivalent daily dose (OMEDD). The six 'Rs' approach to managing high-risk opioid prescribing (Rotation of opioids; Reduction; Replacement pharmacotherapy; Reversal with naloxone; Referral; Restriction of supply) is discussed.

Discussion
The six Rs is an aide-memoire that summarises the management options available to mitigate the risk of high OMEDDs. However, an effective therapeutic alliance between clinician and patient remains the foundation of all risk mitigation strategies.

THE US OPIOID CRISIS, associated with an estimated 130 opioid-related deaths per day,[1] has led to a global shift in the regulation and management of opioid prescribing for chronic non-cancer pain (CNCP).[2] In Australia, Pharmaceutical Benefits Scheme (PBS)–subsidised opioid prescriptions rose from 2.4 million in 1992 to 7.5 million in 2012,[3] with associated increases observed in pharmaceutical opioid-related deaths.[4]

Oral morphine equivalent daily dose (OMEDD) is a marker of analgesic potency, and it allows comparisons between different opioids in terms of their ability to produce the same analgesia as would be expected from a given dose of morphine.[5] Equianalgesic dose conversion is not an exact science: there is a lack of consistency between available conversion charts, and patient-related factors cause further variability.[6] Nonetheless, the Faculty of Pain Medicine, Australian and New Zealand College of Anaesthetists (FPM ANZCA) has produced a free opioid calculator app[7] for this purpose on the basis of its own dose equivalency chart.[8]

Research shows that high-dose opioids are associated with worse functional outcomes[9] and an increased risk of death. One study showed a threefold increase in the risk of death at doses of 200 mg OMEDD,[10] whereas other evidence suggests that an OMEDD of >100 mg elevates the risk of death by a factor of 11.[11] Accordingly, The Royal Australian College of General Practitioners (RACGP) now recommends dose reductions at a threshold of 100 mg OMEDD,[12] which also serves as the trigger for a red flag in the state of Victoria's real-time prescription monitoring system, SafeScript.

The remainder of this article focuses on the management of patients taking opioid doses >100 mg OMEDD for CNCP in a primary care setting, excluding circumstances of acute pain, cancer pain and pain at the end of life. General practitioners and patients need to be aware of the risk of mortality when prescribing or taking an >100 mg OMEDD for CNCP.

Management approaches

The foundation of any risk management intervention is a robust therapeutic alliance. A non-judgemental and person-centred approach is essential to facilitate dialogue about the appropriate use of opioids and their risks.[13] A greater position of safety is secured when patients are prescribed ≤100 mg OMEDD. Opioid tapering or opioid rotation are central to the management of high OMEDDs; however, the management of patient risk associated with high OMEDDs may require additional interventions, such as opioid agonist therapy (OAT) in the context of an opioid use disorder (OUD), the use of naloxone, referral to other health practitioners and the restriction of supply.

Drawing on recommendations identified by Australian and international guidelines for opioid therapy and CNCP,[2,12,14–17] the authors developed the 'six Rs' mnemonic (Box 1) as an aide-memoire for the range of interventions that can be helpful in the management of patient risk associated

with high OMEDD prescribing in the context of CNCP. The six Rs provide a summary of management options available and can be used in any order on the basis of a personalised assessment of the patient's individual circumstances.

Rotation of opioids

Opioid rotation, whereby a patient is switched from one opioid to another,[18,19] may provide a rapid means of reducing OMEDD without loss of analgesic efficacy.[20] Canadian guidance on the use of opioids for CNCP validates the use of opioid rotation as a 'as a way of facilitating ... dose reduction'.[14] Reduction in OMEDD during rotation relies on the fact that patients do not usually show cross-tolerance between opioids.[14] Converting from one opioid to another mandates the use of a reduction in the calculated equianalgesic dose of the second opioid, first to avoid the risks of side effects including respiratory depression and overdose, and also to accommodate the variability of dose conversion charts and patient factors. The elderly, and those with hepatic or renal impairment, have a higher risk of accidental overdose and may require lower doses of the second opioid in an opioid rotation regimen. Drug–drug interactions also must be considered, given the possibility of dramatic fluctuations in serum levels of the second opioid.[19] Such cautious prescribing of the second opioid during an opioid rotation could involve switching to approximately 50–75% of the calculated equianalgesic dose[14,18] of the second opioid.

For example, if a patient were prescribed morphine solution 20 mg three times daily and morphine sulphate controlled-release 60 mg twice daily, then the patient's total OMEDD would be 180 mg. According to the FPM ANZCA, 180 mg is equivalent to 120 mg oxycodone. If one were to prescribe this dose, then the patient, because of a lack of cross tolerance, would likely have side effects including sedation and respiratory depression. It would therefore be prudent to reduce the dose of the second opioid by approximately 25–50% of the calculated equivalent dose, which in this case would be oxycodone 30–45 mg twice daily (or 60–90 mg per day). According to the FPM ANZCA, 60 mg oxycodone is equivalent to 90 mg morphine, while 90 mg is equivalent to approximately 135 mg. This rotation from morphine to oxycodone therefore results in a final total daily dose that is 50–75% of the original dose, significantly reducing the total OMEDD.

Reduction (tapering) of OMEDD

Opioid tapering (ie a gradual reduction in dose over weeks to months) is another method of achieving a reduction in OMEDD for a patient prescribed high-dose opioids.[21,22] For patients prescribed very high OMEDD, tapering may need to follow opioid rotation. Patients can have their dose reduced at a rate of approximately 10% of the starting dose per week (Box 2). GPs may find that opioid reduction templates are a useful resource when planning opioid tapers.[23]

Patient cooperation with opioid tapering is essential, and any decision to taper needs careful explanation of indications, benefits, contraindications and risks. The main indication for opioid tapering is patient safety. It has already been discussed that high OMEDDs of >100 mg can elevate the risk of death;[10,11] however, other considerations, including the side effects of long-term opioid use, may affect the decision to commence tapering (eg opioid-induced hyperalgesia, whereby opioids are responsible for worsening of pain,[24] and opioid-induced hypogonadism[25]).

The indication for long-term opioid use may need to be reviewed in light of recent evidence suggesting that opioids cause more harm and provide less effective analgesia than non-opioid treatment options in the management of osteoarthritis-related pain.[26] Beyond a reduction in the risk of death, there is weak evidence of the benefits of opioid tapering in terms of a reduction in pain and an improvement in function and quality of life.[27] Patients may fear a worsening of pain during a taper; however, this has not been supported by evidence for tapering from a recent Cochrane review.[28]

Tapering should not be considered without specialist input for conditions such as cancer pain, acute pain, and new or ongoing tissue damage.[29] Where there is a diagnosis of OUD, opioid tapering is not considered an alternative to OAT. Because of the risks of opioid withdrawal, tapering during pregnancy is not recommended.[30]

Opioid tapering is associated with concerns regarding the emergence of psychological symptoms or exacerbations of pre-existing psychiatric conditions. The RACGP lists unstable medical and psychiatric conditions as a precaution for opioid tapering.[30] Evidence suggests that patients with a pre-existing diagnosis of depression are more likely to drop out of an opioid taper program, and that those who did drop out of an opioid taper program rated their depressive symptoms as worse than baseline prior to the taper,[31] although it is not clear that the taper itself caused a worsening of depressive symptoms. Nonetheless, the US Centers for Disease Control and Prevention recommends a tapering plan that includes the provision of psychosocial support and monitoring for the emergence of psychological symptoms.[15] However, concern regarding worsening of psychological function or the emergence of anxiety during an opioid

Box 1. The six Rs of managing high-risk opioid prescribing

- Rotation of opioids
- Reduction (tapering)
- Replacement pharmacotherapy
- Reversal with naloxone
- Referral to allied health practitioners/ other specialists
- Restriction of supply

Box 2. Opioid taper

- All opioids (both short- and long-acting) are converted into one long-acting opioid (may involve opioid rotation).
- The dose of the long-acting opioid is decreased at a rate of 10% of the starting dose per week or fortnight.
- The use of short-acting opioids or as-needed doses is strictly limited.
- Non-opioid analgesics are used to manage pain flares.
- Opioid withdrawal symptoms are managed by reducing the taper rate.

taper was not substantiated in a recent Cochrane review of opioid tapering.[28]

Where there is patient distress during an opioid taper – as evidenced by symptoms of dysphoria, fatigue or sleep disturbance – chronic opioid withdrawal needs to be considered.[32] Such symptoms need to be managed in a caring therapeutic relationship and may necessitate a reduction in the speed of the taper. Benzodiazepines are not recommended for the management of anxiety during a taper.[23] It is recommended that addiction specialist advice be sought on this issue; however, in most cases, persisting with tapering is worthwhile given the risks associated with opioid doses above 100 mg OMEDD.

Replacement pharmacotherapy (opioid agonist therapy)

It has been estimated that up to 30% of patients prescribed long-term opioids develop aberrant behaviours related to their prescription opioids (eg medically unsanctioned use, dose escalation, lost prescriptions or prescription forgery).[33] In such cases, it is important to consider the diagnosis of an OUD as defined by the *Diagnostic and statistical manual of mental disorders*, fifth edition.[34] Patients presenting with symptoms of OUD are likely to benefit from OAT with buprenorphine or methadone.[17] Where a patient with an OUD refuses OAT, addiction specialist advice should be sought. Each state and territory in Australia provides accredited pharmacotherapy prescribing training for clinicians covering clinical issues, practical considerations and local regulations.

Reversal with naloxone

High-dose opioids carry a risk of overdose and respiratory depression. The Community Overdose Prevention Education program provides training on harm reduction interventions, including the use of naloxone.[35] Naloxone, a mu-opioid receptor antagonist, reverses the effects of opioid overdose.[36] In Australia it is available as a vial, prefilled syringe or nasal spray. Naloxone, and accompanying training on its administration, should be offered to all patients who are at risk of opioid overdose, including those on high-risk opioid medications.[9] Guidance suggests that the threshold for considering naloxone supply should be 50 mg OMEDD.[2] Training can be as basic as identification of features of toxicity and the administration of intranasal or intramuscular naloxone.[37]

Table 1. Addiction specialist telephone advisory services*

State or territory	Service	Telephone number
Victoria	Drug and Alcohol Clinical Advisory Service	1800 812 804
Tasmania	Drug and Alcohol Clinical Advisory Service	1800 630 093
Northern Territory	Drug and Alcohol Clinical Advisory Service	1800 111 092
South Australia	Drug and Alcohol Clinical Advisory Service	(08) 7087 1742
Western Australia	Clinical Advisory Service	(08) 9442 5042
New South Wales/Australian Capital Territory	Drug and Alcohol Specialist Advisory Service	(02) 9361 8006
Queensland	Alcohol and Drug Clinical Advisory Service	1800 290 928

**General practitioners wishing to speak with an alcohol and other drug (AOD) specialist for secondary advice may contact their local AOD service or their state's telephone AOD specialist consultancy service. These numbers are not for patients and are for use by health professionals only.*

Referral

Referral to psychologists, physiotherapists and other allied health practitioners should be encouraged as part of a multimodal system of CNCP management,[38] given that psychological and physical therapies can help de-emphasise the role of prescribed opioids. Referral to an accredited pharmacist for a Domiciliary Medication Management Review facilitates a comprehensive assessment of the overall safety of prescribing and facilitates further discussion regarding prescribing options.[16] Referral to a psychologist or a psychiatrist should be considered where there are mental health comorbidities, complex emotional trauma, poor coping skills and pain-catastrophising.[39] Referral to an addiction specialist or a pain physician can help inform long-term plans, such as initiation of pharmacotherapy or opioid reduction strategies. Free, confidential addiction specialist advice is also available across all Australian jurisdictions (Table 1).

Restriction of supply

It is not mandatory to prescribe standard PBS quantities of opioids. Reduced quantities can be prescribed when there is a concern regarding high-dose opioid use.[40] This approach facilitates increased frequency of face-to-face consultations with the prescriber, thereby enhancing monitoring of opioid therapy. Limited dispensing,[41] whereby patients attend a pharmacy regularly to receive staged quantities of medication (eg daily or weekly), allows the pharmacist to monitor medication consumption patterns. Limited dispensing is a cornerstone of OAT and can be a useful intervention for patients in receipt of high-risk opioid prescriptions.

Conclusion

Patients prescribed opioids at doses >100 mg OMEDD have an elevated mortality risk. The 'six Rs' aide-memoire, based on current national and international guidelines, offers an easy-to-remember mnemonic of risk mitigation

strategies for the management of high-risk opioid prescribing. However, such approaches are underpinned by a robust therapeutic alliance between the doctor and their patient.

Key points

- The use of high-dose opioids (>100 mg OMEDD) in the management of CNCP increases the risk of death.
- Patients prescribed high doses of opioids need to be managed appropriately to reduce risks of morbidity and mortality.
- The foundation of any risk management strategy is the therapeutic alliance between the patient and the clinician.
- The 'six Rs' mnemonic may help clinicians implement interventions that reduce the risks associated with >100 mg OMEDD.

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