Calling time on the use of modified-release opioids for acute pain

The first modified-release (MR) formulation of oxycodone was approved for the management of pain in 1995 and aggressively marketed (with false claims of a low addiction risk) primarily for the management of chronic non-cancer pain.[1] In many high income countries, including Australia,[2] prescription of MR oxycodone for the management of acute pain, especially post-operative pain, then became commonplace.[1] This occurred despite no evidence at the time showing that MR oxycodone was better — in terms of analgesia and/or adverse effects — than immediate-release (IR) oxycodone alone (as explained below).[1,3,4] A survey of Australian public and private hospital pharmacists showed that MR opioids were commonly prescribed to opioid-naïve patients with acute pain in more than 70% of hospitals — both as an inpatient and at discharge.[2]

Guidelines reflecting the current evidence base and aiming to improve the safety of opioid use for acute pain management in Australia have recently been introduced.[5,6] These strongly recommend against the initiation of MR opioids for acute pain in opioid-naïve patients. Opioids remain an important part of multimodal acute pain analgesic regimens, with guidelines indicating how to use IR opioids more safely and effectively, while not limiting appropriate access and dosing for patients who require them.

Calling time on initiating MR opioids for acute pain is a key recommendation of these guidelines and aims to reduce opioid risk in two key areas: in-hospital morbidity and mortality, and inadvertent persistent post-discharge opioid use (PPOU), which comes with its own list of potential adverse effects.[7]

Recent changes to opioid-prescribing guidelines in Australia

In 2000, regulatory changes made by the Australian Therapeutics Goods Administration were designed to decrease the risk of harm from prescription opioids.[8] Included in the changes were that MR opioids should not be used for the management of severe pain unless the pain is opioid-responsive and "requires daily, continuous, long term treatment" (thus excluding acute pain).[8] In 2022, the Australian Commission on Safety and Quality in Health Care published their Opioid Analgesic Stewardship in Acute Pain Clinical Care Standards, which advised that MR opioid use for the management of acute pain "should be exceptional and not routine".[5] In the same year, a new Choosing Wisely Australia statement said "Avoid routine prescription of slow-release (SR) opioids in the management of acute pain, in hospital and community settings, unless there is a demonstrated need, close monitoring is available, and a cessation plan is in place".[9] A 2023 publication from the Australian and New Zealand College of Anaesthetists and Faculty of Pain Medicine contains similar recommendations,[6] which are consistent with other Australian[10,11] and international guidelines.[7,12-14]

Although most of the literature on the topic involves acute pain management in inpatients, there is no reason to think that MR opioids would be any more effective or safer when used for non-surgical acute pain, or acute pain in the community when appropriate and reliable monitoring is not available. Two Australian guidelines do not specify the acute pain setting when advising that MR opioids not be used.[9,11]

The most recent Australian guidance documents recommend that, if an opioid is indicated for the management of acute pain, an IR and not MR opioid should be commenced. This does not mean that IR opioid regimens are without risk of patient harm; however, risks can be mitigated through appropriate dosing and safer monitoring practices.

Benefits and risks of immediate-release compared with modified-release opioids

Despite the popularity of MR opioid prescription for the management of acute pain, there are few head-to-head trials comparing IR and MR opioids (especially the same opioid).[15]

In some countries, but not Australia, IR oxycodone is available as a tablet containing both oxycodone and paracetamol. This combination tablet limits the amount of oxycodone that can be given because of recommended maximum daily doses of paracetamol. Therefore, MR oxycodone should be compared with oxycodone alone. There was no good evidence to support the idea that MR oxycodone was superior to IR oxycodone alone when prescribing of MR oxycodone for acute pain started to become common practice.[3,16] One study reporting significantly better pain relief and fewer adverse effects associated with the use of MR compared with IR oxycodone alone was retracted a decade later because of scientific fraud.[17]

Recent Australian publications show that, compared with IR opioids, use of MR formulations (with or without additional IR opioid as needed) for the management of acute post-operative pain actually leads to less effective pain relief, higher opioid dose requirements, an increased risk of opioid-related adverse events, increased lengths of hospital stay, and higher 28-day readmission rates.[3,4,15,18] The risk of falls is also increased.[4] Older patients may be at particular risk because of age, comorbid conditions, or concurrent medications.[19] MR opioid formulations have also been associated with more frequent opioid-related adverse events after hospital discharge.[20]

The risk of PPOU, where opioids are continued for longer than 30 days after initial prescription for acute

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pain, is higher in patients given MR compared with IR opioids.[6,7] Estimates of new long term opioid use after opioids have been prescribed for post-operative pain vary from less than 1% to 13%; however, the risks may be greater the longer the duration of initial use and with higher doses.[12] An Australian study reported a fivefold greater risk of PPOU in opioid-naïve patients discharged with MR+IR (5%) compared with IR opioids only (1%).[21]

Compared with IR opioids, the risk of opioid-induced ventilatory impairment (OIVI) is also increased when MR opioids are prescribed for the management of acute pain.[7]

Marketing of MR opioids promoted the ideas of easy 12-hourly dosing schedules and constant plasma concentrations leading to sustained pain relief.[22] However, acute pain is not constant and the slow onset and offset of MR opioids means doses cannot be rapidly and safely titrated for each patient — neither up-titrated to better cover severe episodes of acute pain associated with activity, nor down-titrated as opioid requirements decrease as the patient recovers or if the patient has severe opioid-related adverse effects.[19,22]

The aim of good acute pain management is to assist with recovery and return of patient function. The faster onset and shorter duration of action of IR opioid

Titration of immediate-release opioids prescribed for the treatment of acute pain[6,10,11,19,22-24]

	Requirements for individualised opioid titration regimens
The opioid prescription	• The initial dose range of opioid prescribed should vary according to the age of the patient (for opioid-naïve patients) and the severity of the anticipated pain: ▸ Age is a better predictor of opioid requirements than patient weight ▸ Increasing age is associated with decreased opioid requirements and this appears to be primarily due to pharmacodynamic rather than pharmacokinetic factors; that is, increased sensitivity of the central nervous system with ageing rather than the changes in metabolism and excretion of the drug that might also be seen in older patients ▸ The initial opioid dose range prescribed should be lower in patients with moderate pain than those with severe acute pain; lower doses may also be safer where appropriate monitoring is not reliable • Subsequent doses may need to be adjusted according to patient response (analgesic effectiveness and adverse effects) • Prescribe an appropriate dose interval (the interval within which additional doses should not be given): ▸ In some settings (eg, where there is 24-hour medical cover and experienced nursing staff and appropriate monitoring are available) it may be reasonable to order an IR opioid "every two hours as needed"; in other settings "every four hours as needed" may be safer • Order "as needed" only and not on a regular (time-contingent) basis; write maximum 24-hour dose as "sedation score less than 2" • The IR opioid should be used for the shortest time possible and in decreasing doses over a short time. Deprescribing starts in hospital and requires involvement of nurses, doctors, ward pharmacists and the patient: ▸ This requires regular patient review ▸ The opioid prescription may need to be rewritten to allow for or assist with decreasing opioid dose trajectories, sometimes on a daily basis
Assessment of analgesic effectiveness	• Unidimensional pain scores are commonly used in the acute pain setting to determine analgesic effectiveness and guide opioid titration: ▸ Do not adjust analgesic regimens, including opioid doses, based on a patient's pain scores alone ▸ Predictors of high pain scores include psychological comorbid conditions (eg, anxiety, catastrophising), pre-existing chronic pain, and tolerance to opioids, and therefore high scores do not always mean that an opioid — or more opioid — is needed ▸ A patient's pain score trajectory (plotting a patient's pain scores over time) is a more useful indicator of patient progress and can allow identification of psychological distress, the presence of non-opioid-responsive pain and post-operative/post-trauma complications; pain score trajectories that do not decrease over the first few days are also good predictors of chronic post-surgical pain. Patients whose pain score trajectories are not decreasing require review ▸ "Chasing" pain scores with opioids to achieve an arbitrarily defined acceptable level of pain or zero pain can lead to increases in the risk of OIVI and PPOU • Include an assessment of patient function (eg, using functional activity scores). One example of a functional activity score is: ▸ A — no limitation of relevant activity due to pain (relative to baseline) ▸ B — mild limitation of activity due to pain ▸ C — unable to complete activity due to pain
Recognition and management of OIVI	• Increasing sedation is a more reliable indicator of developing OIVI than a decrease in respiratory rate: ▸ Respiratory rate can remain within acceptable limits even when OIVI is severe ▸ Record sedation scores (along with pain scores and functional activity scores) at time of administration of the IR opioid and when peak effect is expected (ie, about one hour after administration of an oral IR opioid) • One suggested sedation scoring system is: 0 = wide awake, 1 = easy to rouse (and can stay awake), 2 = easy to rouse but unable to remain awake, and 3 = difficult to rouse: ▸ Titrate opioids so that sedation score is always < 2 • Hypoxaemia may be a very late sign of hypoventilation, especially if the patient is receiving supplemental oxygen • Immediate intervention is required if a patient has a sedation score of 2 or 3, regardless of the patient's respiratory rate

IR = immediate-release; MR = modified-release; OIVI = opioid-induced ventilatory impairment; PPOU = post-discharge opioid use. ◆

formulations enables more rapid and safer titration of opioid doses to better match patient needs.[19] That is, titration of IR opioids can more rapidly cover the considerable and often rapid variations in pain intensity that may be experienced by patients with acute pain.[22] Regular use of non-sedating analgesia agents, including simple analgesics, and local anaesthetic techniques, where indicated, provides a sustained and opioid-sparing background level of analgesia.

Improving the effectiveness and safety of immediate-release opioid regimens

Concerns about opioid use should not lead to underprescription for patients with acute pain where there is an appropriate need. There needs to be an evidence-based move towards maximising safety and efficacy in prescribing, by limiting commencement of MR opioids while advocating for appropriate dosing of IR opioids.

Just as MR opioid regimens fail to enable adequate titration in a patient with acute pain, so do some IR opioid regimens, especially when prescribed doses are inappropriate (including underdosing) or dose intervals are too long. There is, unfortunately, a lack of good evidence to support the best way to use IR opioids in the acute pain setting. However, a number of consensus-based Australian guidelines have been published and should be considered for use.[6,10,11,23]

For IR opioid regimens to be as safe and effective as possible, they need to be titrated to individual patient needs. A "one size fits all" prescription will not be appropriate for all patients, and inadequate monitoring and a lack of individual dose titration, as well as a failure to intervene quickly should the patient show signs of OIVI, can lead to patient harm. Suggested requirements for individualised opioid titration regimens are described in the Box.

Atypical opioids (meaning their analgesic effect does not only result from μ-opioid-receptor activation), including tapentadol, tramadol and buprenorphine, are increasingly prescribed in the acute pain setting. At equianalgesic doses, the risks of OIVI from IR tapentadol and tramadol are less compared with conventional μ-agonist opioids such as oxycodone.[19] There is no difference in the incidence of OIVI in patients given parenteral or sublingual buprenorphine compared with conventional opioids.[19] Coprescription of more than one opioid increases the risk of OIVI; this includes coprescription of a conventional and atypical opioid (eg, tapentadol and oxycodone).[7] A dosing interval for one opioid makes little sense in the context of coprescription of more than one opioid where there is no guidance about intervals between them.

Conclusions

The widespread use of MR opioids in acute pain occurred despite the lack of any good evidence of benefit compared with IR opioids. Patients should be prescribed adequate initial age- and condition-appropriate IR doses that are then titrated to the variable levels of pain that occur throughout the acute pain period, with close monitoring, particularly for excessive sedation. The literature clearly shows that MR opioid use in acute pain is associated with less effective pain relief and a greater risk of patient harm. Although continuing pre-operative long term MR opioids is good practice, MR opioids should no longer be routinely initiated for management of acute pain.

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1 Macintyre PE, Quinlan J, Levy N, Lobo DN. Current issues in the use of opioids for the management of postoperative pain: a review. *JAMA Surg* 2022; 157: 158-166.

2 Society of Hospital Pharmacists of Australia. Reducing opioid-related harm: a hospital pharmacy landscape paper. Melbourne: SHPA, 2018. https://www.shpa.org.au/publicassets/b2e943ca-de53-ec11-80dd-005056be03d0/shpa_-_reducing_opioid_related_harm.pdf (viewed Feb 2020).

3 Liu S, Athar A, Quach D, et al. Risks and benefits of oral modified-release compared with oral immediate-release opioid use after surgery: a systematic review and meta-analysis. *Anaesthesia* 2023; 78: 1225-1236.

4 Liu S, Patanwala AE, Naylor JM, et al. Impact of modified-release opioid use on clinical outcomes following total hip and knee arthroplasty: a propensity score-matched cohort study. *Anaesthesia* 2023; 78: 1237-1248.

5 Australian Commission on Safety and Quality in Health Care. Opioid Analgesic Stewardship in Acute Pain Clinical Care Standard — acute care edition. Sydney: ACSQHC, 2022. https://www.safetyandquality.gov.au/publications-and-resources/resource-library/opioid-analgesic-stewardship-acute-pain-clinical-care-standard (viewed Apr 2022).

6 Australian and New Zealand College of Anaesthetists and Faculty of Pain Medicine. PS41(G) position statement on acute pain management. Melbourne: ANZCA, 2023. https://www.anzca.edu.au/getattachment/558316c5-ea93-457c-b51f-d57556b0ffa7/PS41(G)-Position-statement-on-acute-pain-management-2023#page= (viewed Oct 2023).

7 Levy N, Quinlan J, El-Boghdadly K, et al. An international multidisciplinary consensus statement on the prevention of opioid-related harm in adult surgical patients. *Anaesthesia* 2021; 76: 520-536.

8 NPS MedicineWise. Opioids: new and amended PBS listings. Sydney: NPS MedicineWise, 2020. https://www.nps.org.au/radar/articles/opioids-new-and-amended-pbs-listings (viewed Aug 2023).

9 Choosing Wisely Australia. Avoid routine prescription of slow-release opioids in the management of acute pain unless there is a demonstrated need, close monitoring is available and a cessation plan is in place. Choosing Wisely Australia, 2022. https://www.choosingwisely.org.au/recommendations/fpm7 (viewed Dec 2022).

10 Australian Medicines Handbook. Australian Medicines Handbook. www.amh.net.au (viewed Jan 2020).

11 Therapeutic Guidelines. Pain and analgesia. https://tgldcdp.tg.org.au/guideLine?guidelinePage=Pain+and+Analgesia&frompage=etgcomplete (viewed Oct 2021).

12 Dowell D, Ragan KR, Jones CM, et al. CDC clinical practice guideline for prescribing opioids for pain — United States, 2022. *MMWR Recomm Rep* 2022; 71: 1-95.

13 Chou R, Gordon DB, de Leon-Casasola OA, et al. Management of postoperative pain: a clinical practice guideline from the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council. *J Pain* 2016; 17: 131-157.

14 Srivastava D, Hill S, Carty S, et al. Surgery and opioids: evidence-based expert consensus guidelines on the perioperative use of opioids in the United Kingdom. *Br J Anaesth* 2021; 126: 1208-1216.

15 Tan AC, Bugeja BA, Begley DA, et al. Postoperative use of slow-release opioids: the impact of the Australian and New Zealand College of Anaesthetists/Faculty of Pain Medicine position statement on clinical practice. *Anaesth Intensive Care* 2020; 48: 444-453.

16 Cheung CW, Ching Wong SS, Qiu Q, Wang X. Oral oxycodone for acute postoperative pain: a review of clinical trials. *Pain Physician* 2017; 20: SE33-SE52.

17 Shafer SL. Postoperative analgesia with controlled-release oxycodone for outpatient anterior cruciate ligament surgery [notice of retraction]. *Anesth Analg* 2009; 108: 1350.

18 Awadalla R, Liu S, Kemp-Casey A, et al. Impact of an Australian/New Zealand organisational position statement on extended-release opioid prescribing among surgical inpatients: a dual centre before-and-after study. *Anaesthesia* 2021; 76: 1607-1615.

19 Schug SA, Palmer GM, Scott DA, et al. Acute pain management: scientific evidence, 5th edition. Melbourne: Australian and New Zealand College of Anaesthetists and Faculty of Pain Medicine, 2020. https://www.anzca.edu.au/safety-advocacy/advocacy/college-publications (viewed Dec 2020).

20 Herzig SJ, Anderson TS, Jung Y, et al. Risk factors for opioid-related adverse drug events among older adults after hospital discharge. *J Am Geriatr Soc* 2022; 70: 228-234.

21 Lam T, Xia T, Biggs N, et al. Effect of discharge opioid on persistent postoperative opioid use: a retrospective cohort study comparing tapentadol with oxycodone. *Anaesthesia* 2022; 78: 420-431.

22 Quinlan J, Levy N, Lobo DN, Macintyre PE. No place for routine use of modified-release opioids in postoperative pain management. *Br J Anaesth* 2022; 129: 290-293.

23 NPS MedicineWise. Safe use of opioids in acute pain. Sydney: NPS MedicineWise, 2022. https://www.nps.org.au/safe-use-of-opioids-in-acute-pain (viewed Dec 2022).

24 Macintyre PE, Schug SA. Acute pain management a practical guide, 5 ed. CRC Press, Taylor and Francis Group; 2021. ■