Routine use of modified-release opioids on hospital discharge can no longer be justified

We read with interest the study by Lam et al. [1]. This was a retrospective cohort study conducted in four large private hospitals in Australia comparing persistent postoperative opioid use (defined as a current prescription at 90 days following hospital discharge) in surgical patients prescribed immediate release, or modified formulations, of either oxycodone or tapentadol on hospital discharge. Oxycodone is a synthetic opioid with a well-documented role in contributing to the global opioid crisis, whilst tapentadol is a newer 'atypical' drug. It is noteworthy that Seqirus Pty Ltd. funded the study and is also the manufacturer of tapentadol.

Lam et al. included 120,000 patients in their analysis. They demonstrated the following: the risk of persistent postoperative opioid use was lowest in opioid naïve patients prescribed immediate release opioid rather than modified release opioids, "*For opioid-naive patients receiving immediate release opioids, there was no significant effect of opioid type*", and that both modified-release tapentadol and oxycodone were associated with more persistent postoperative opioid use than immediate release preparations of the two opioids; however, modified-release oxycodone was marginally more associated with persistent postoperative opioid use than modified-release tapentadol.

We therefore argue that the conclusion that there "*appeared to be lower odds of persistence for tapentadol compared with oxycodone among key subgroups*" is misleading. The lower odds of persistence of opioid use only occurred when modified-release tapentadol was compared with modified-release oxycodone, and was not statistically significant when comparing immediate-release formulations. This distinction is important as the use of postoperative modified-release opioids is no longer recommended by many worldwide societies due to the risk of persistent postoperative opioid use and opioid-induced ventilatory impairment [1–5]. Indeed, the findings add to the body of evidence that the use of modified-release opioids is a significant driver for persistent postoperative opioid use, and that surgical patients should only receive immediate-release formulations of opioids. The study does, however, demonstrate that patients taking modified-release oxycodone have the highest risk of persistent postoperative opioid use. This is unsurprising as modified-release oxycodone is the archetypal opioid that caused the opioid epidemic. Like all modified-release opioids, modified-release oxycodone is difficult for patients to wean from, but the intrinsic likeability of oxycodone, as well as the short duration of action of modified-release oxycodone, further increases the risk of persistent postoperative opioid use [2] (Table 1).

Persistent post-surgical opioid use is not without risks. It is associated with increased risk of death from opioid-induced ventilatory impairment and increase risk of harm from other opioid-related adverse drug events, including susceptibility to infection; falls and trauma, failed operations, opioid-induced hyperalgesia and chronic pain states [5].

The knowledge base against the utilisation of postoperative prescription of modified-release opioids on hospital discharge is now overwhelming; the use of modified-release opioids is associated with worse pain control, higher opioid consumption, as well as harms from higher rates of persistent postoperative opioids use and opioid-induced ventilatory impairment [1–5]. Consequently several regulatory and national bodies, including the US Food and Drug Administration, the US Centers for Disease Control and Prevention, Australia's Faculty of Pain Medicine and Australia's Therapeutic Goods Administration now advise against the use of modified-release opioids, except for long term treatment of pain [2-5]. In a similar manner, and with the intention of reducing the risk of inadvertent persistent postoperative opioid use and opioid-induced ventilatory impairment, other regulatory bodies, including the Medicines and Healthcare products Regulatory Agency in the UK, must review the literature and make recommendations on the use of modified-release opioid preparations for the management of self-limiting acute pain.

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Table 1. Pharmacological properties of modified-release oxycodone that predispose to persistent postoperative opioid use (PPOU) [2-5].

	Issues	**Implication**
Generic properties of modified-release opioids that increase the risk of PPOU	Inability to titrate down as pain recedes. False assumption that postoperative pain has a flat trajectory, until opioids are no longer required. Increase complexity of postoperative opioid weaning and deprescribing	Misuse with modified release opioid preparations is easier to slip into.
Pharmacodynamic properties of oxycodone that further increase the risk of PPOU	Very likeable opioid and fewer side effects	Misuse of oxycodone is easy to slip into.
Pharmacokinetic properties of modified release oxycodone that further increase the risk of PPOU	Biphasic release causing a peak and trough. Duration of action is only approximately 7 hours in many patients	Unexpected pain when the opioid predictably wears off before the next dose is due. This can lead to either dose escalation or requirement for further opioid therapy. Thus, opioid tapering is more difficult.