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Editorial

Tapentadol and the opioid epidemic: a simple solution or short-lived sensation?

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The `opioid epidemic´ has received global attention. During the COVID-19 pandemic, the annual overdose death rate in the USA increased to over 100,000 [1]. Although the highest opioid overdose death rates around the world are concentrated in certain countries, the USA and Canada in particular [2], the populations of many other countries including the UK and Australia are also suffering [3].

While prescription opioids contribute meaningfully to the problem, most opioid overdose deaths in recent years arise from illicit synthetic opioids [4], and governmental agencies have taken action to curb opioid overprescribing in healthcare settings. Following the publication of the Centers for Disease Control and Prevention Guideline for Prescribing Opioids for Chronic Pain in 2016 [5], nearly every state in the USA within 2 years had codified laws restricting the prescription of opioid analgesics based on dosage or days of therapy [6]. Most of these laws were broad and applied to acute pain indications including pain after surgery, despite the guideline specifically identifying post-surgical pain as ``*outside the scope*´´ of the guideline, though it appears state laws had little impact on prescribing behaviour after surgery [7]. In the UK, the Medicines and Healthcare products Regulatory Agency issued a drug safety update warning of the risk of dependence and addiction related to opioids and providing recommendations to prescribing clinicians [8]. These recommendations specifically advise clinicians to: educate every patient who is prescribed opioids about the risks of tolerance and accidental overdose and death; provide `regular monitoring and support´ during therapy; taper the dosage of opioids with the goal of cessation; and monitor for hyperalgesia in the event of increased pain and/or persistent opioid use [8].

In the peri-operative period, anaesthetists are leaders in pain management and are well positioned to make a positive impact on opioid prescribing after surgery. The average reported rate of new persistent postoperative opioid use after minor surgeries of 6% makes this problem arguably the most common major postoperative complication [9]. Of great concern is the fact that surgeon-prescribed opioids transition to long-term prescriptions for opioids by primary care clinicians within several weeks of surgery if postoperative opioid cessation is not successful [10]. Persistent opioid use has been shown to be associated with increased healthcare utilisation and costs [11, 12], as well as the development of opioid use disorder, overdose and death [12, 13]. Hence, interventions and treatments to prevent persistent opioid use are of critical importance.

Post-surgical opioid use

In this issue of *Anaesthesia*, Lam et al. report the results of a retrospective cohort study, involving patients discharged from surgical wards at four large private hospitals, which analysed prescription data for the rates of persistent postoperative opioid use based on two types of commonly prescribed opioids in Australia, either oxycodone or tapentadol [14]. The investigators focused on two major factors in their grouping: whether patients were opioid-naive or opioid-experienced; and whether patients were prescribed immediate release opioids alone or in combination with modified release opioids, which represent a long-acting formulation of opioids. Opioid-naive was defined as no active opioid prescription within 90 days before surgery; all others were considered opioid-experienced. In addition, they performed a subgroup analysis involving only orthopaedic surgical patients using the same grouping.

Persistent postoperative opioid use at 3 months was the primary outcome and defined as any active opioid prescription at 90 days after discharge from the hospital after surgery with no more than a 60-day gap in between active opioid prescriptions. In the key results, over 120,000 patients were included in the analysis, and approximately 80% were opioid-naive at the time of surgery. Of the opioid-naive patients, 2.3% were identified by the investigators as having persistent postoperative opioid use at 3 months while 27.2% of opioid-experienced patients had persistent postoperative opioid use. Among opioid-naive patients, two-thirds received immediate release opioids only while one-third, or over 30,000, patients received modified release opioids. In the general sample of all surgical patients who received modified release opioids, both opioid-naive and opioid-experienced, those who received tapentadol had lower odds of persistent postoperative opioid use at 3 months compared with those who received oxycodone.

In the subgroup of 19,832 orthopaedic surgical patients, 73% were opioid-naive at the time of surgery. Those prescribed tapentadol had lower odds of persistent postoperative opioid use at 3 months compared with oxycodone regardless of pre-operative opioid status or formulation prescribed.

We finally have the answer to the opioid epidemic: prescribe tapentadol and call it a day. There is a quote attributed to H. L. Mencken that applies here: ``*For every complex problem, there is an answer that is clear, simple and wrong*.'' While there are useful inferences from the study by Lam et al., preferentially prescribing one opioid drug over another is not the answer, and there are several critical limitations to their study. Importantly, association is not causation. While there may be an association between tapentadol and lower odds of persistent postoperative opioid use in orthopaedic surgery patients regardless of pre-operative opioid status or formulation prescribed, we cannot attribute the cause to tapentadol because the grouping of patients was not randomly assigned. We do not know why clinicians chose to prescribe one type of opioid over the other and which factors may have influenced that decision. One possible source of bias could be that those who chose tapentadol saw it as a `safer´ opioid when compared with oxycodone which has been well-publicised for its addictive potential.

The concept of using tapentadol as the primary opioid for post-surgical pain is novel and may be a part of the solution to the complex problem of persistent opioid use. Tapentadol is different from classic opioids in that it is both a μ-opioid receptor agonist and a norepinephrine reuptake inhibitor [15]. In contrast to another atypical opioid tramadol, tapentadol is not a pro-drug, and does not have the variable effects of tramadol ranging from no analgesic effect in poor metabolisers to the rapid high concentrations seen in ultrarapid metabolisers [16]. In addition to central norepinephrine re-uptake inhibition, tramadol blocks re-uptake of serotonin, which can cause side effects and major adverse effects such as serotonin syndrome, without clear analgesic benefit. By comparison, the more predictable re-uptake inhibition of norepinephrine by tapentadol offers greater potential for analgesia, including among persons with mixed neuropathic, nociplastic and nociceptive pain states, and potentially a synergistic effect with the μ-opioid receptor agonism. The immediate release version of tapentadol offers similar analgesic properties to oxycodone; however, due to its complex pharmacology, the comparisons must be made in terms of equal analgesia, rather than opioid equivalents. Whereas the market share of tapentadol in the USA is low, the limited available data suggest less misuse and abuse of tapentadol when compared with other traditional opioids.

Pain management

We are also missing key information regarding the context of inpatient pain management at the study sites. We do not know if patients were managed by an acute pain service, whether or not they received regional analgesia and nerve blocks or even if multimodal analgesia was used. Multimodal analgesia and involvement of an inpatient pain service, especially in complex cases (e.g. opioid-tolerant patients), are recommendations included in the *Surgery and Opioids: Best Practice Guidelines 2021* from the Faculty of

Pain Medicine and Royal College of Anaesthetists in collaboration with other UK medical professional societies [17]. In addition, we do not know how analgesic administration was guided in terms of validated pain assessment tools [18], and we do not have any data on recovery and pain resolution trajectories [19, 20]. At the time of discharge, a crucial piece of key information missing is the discharge opioid protocol and whether or not there was provision of clear guidance to patients and caregivers on tapering of opioids to cessation [18, 21]. Patient education on de-escalation of opioids, potential hazards of taking opioids and safe storage of opioids is also recommended by the Faculty of Pain Medicine's guidelines [17]. Finally, the use of prescription data does not provide us with an accurate assessment of actual opioid consumption.

Although the use of modified release tapentadol was associated with lower odds of persistent postoperative opioid use compared with modified release oxycodone in opioid-naive patients, we would argue strongly against any initiation of any modified release opioids in this patient population. An international consensus recommends against initiation of modified release opioids in the peri-operative period, citing evidence of no benefit over immediate release formulations, increased risk of opioid-related ventilatory impairment and higher rates of persistent postoperative opioid use [22]. The Faculty of Pain Medicine's guidelines allow for modified release opioids but only if a pain medicine specialist is consulted first [17]. The observation that one-third of opioid-naive patients in the study cohort received any modified release opioid is concerning in our collective opinion and represents an opportunity for improvement.

When considering opioid stewardship programmes in the context of the opioid epidemic, what is often lost is the discussion of pain management. Anaesthetists, surgeons and other peri-operative clinicians would generally agree today that over-reliance on opioid pain management is not ideal for patients. However, tremendous `unwarranted variation´ continues to exist globally in the management of acute peri-operative pain as seen in the various opioid prescriptions and combinations, including multiple opioid drugs, shown in the present study. `Unwarranted variation´ is simply defined as the clinical practice differences that cannot be explained by patient factors, patient preference or existing evidence [23].

An important initiative launched in the USA is the establishment of common principles of acute peri-operative pain management, which have been developed collaboratively by 14 medical organisations [18]. These seven principles set the foundation for better pain management for all surgical patients and provide the means to address unwarranted variation (Table 1).

Changing practice

Implementing these principles is the exact opposite of a simple solution, but it makes the most sense. Setting these up on a broad scale is going to take a tremendous amount of effort, resources and time. If that is not enough, the work does not stop at discharge. Decreasing persistent postoperative opioid use will also require something that is not included in these seven principles: patient surveillance in the subacute period after surgery. The time to cessation of postoperative opioids is highly variable, and some patients, such as those on modified release formulations at the time of surgery, are more likely to stay on opioids long term [24]. To effectively prevent surgical prescriptions for opioids from transferring to primary care and the resultant persistent postoperative opioid use, the time to intervene is within the first 3 months of surgery [10]. This domain is far beyond the typical anaesthesia or acute pain service, but the duration of < 3 months does not meet the definition of chronic pain [25]. Yet, persistent postoperative opioid use may arguably begin before the 3-month mark for certain surgical populations [26]. This is the rationale for the `transitional pain service´ to fill in this gap in care [27, 28]. Although a transitional pain service is not included in the Faculty of Pain Medicine's guidelines, there is a recommendation that any previously opioid-naive patient still on opioids at 90 days

Table 1 Seven principles for effective acute peri-operative pain management (adapted from [18]).

Principle 1	Careful pre-operative evaluation with consideration of postoperative pain history, chronic pain, substance use disorder and other comorbidities
Principle 2	Utilisation of validated pain assessment tools, not only pain intensity, to guide pain management and adjust treatment
Principle 3	Routine administration of multimodal analgesia, including regional anaesthetic techniques when indicated and available
Principle 4	Education on pain management designed specifically for patients and caregivers
Principle 5	Education on tapering, proper storage and disposal of opioids designed specifically for patients and caregivers
Principle 6	Individualisation of pain management based on analgesic effectiveness and/or adverse effects of therapies
Principle 7	Access to a pain medicine specialist especially for postoperative pain that is greater than expected or for patients with complex pain histories

postoperatively be evaluated by a primary care physician or pain medicine specialist for possible chronic post-surgical pain [17].

If all of this sounds like a lot more work than just changing the prescribed discharge opioid to tapentadol, that is because it is. However, these major investments in overhauling the paradigm of peri-operative pain management are likely the best opportunity to meaningfully improve the quality of pain management for surgical patients and decrease unnecessary opioid use.

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