Editorial

Preoperative opioid use: a modifiable risk factor for poor postoperative outcomes

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"And far and wide, in a scarlet tide, the poppy's bonfire spread"

Bayard Taylor (1825-1878)

Patients with chronic pain taking long-term opioids presenting for surgery are more likely to have a turbulent perioperative course than their opioid-naïve counterparts. Their postoperative pain can be more challenging to manage,[1] and they have a higher risk of opioid-induced ventilatory impairment and persistent postoperative opioid use.[2]

In addition, there are some less well-known adverse effects of long-term opioid therapy that can impact on short- and long-term postoperative outcomes. These may affect both the patient in terms of complication rates and postoperative recovery trajectories, and the health care system in terms of costs, including those related to longer hospital stay. Some of these adverse outcomes may be related to the recognised immunosuppressive effects of opioids, and to opioid-related endocrinopathies.

There has been a significant increase in the number of patients who have been prescribed opioids over the past 30 years[1] particularly for the treatment of chronic non-cancer pain, and many of these patients will be presenting for surgery. Patients awaiting elective surgery (e.g., total joint arthroplasty) may be on a waiting list for some time – prolonged further due to the impact of the Covid-19 pandemic – which presents an opportunity to address existing long-term opioid use and mitigate the risks.[3]

Long-term preoperative opioid use and adverse postoperative outcomes

Numerous recent publications have shown that long-term preoperative opioid use is associated with a higher risk of both short-and long-term adverse postoperative outcomes after a number of different types of surgery.[4-14] These include increased rates of surgical

infection and revision surgery, higher readmission rates, longer lengths of hospital stay and higher medical costs after surgery (**Table 1**).[4-14]

The risk of some of these poorer outcomes (e.g., length of hospital stay, surgical infection and revision rates, readmission rates, medical costs after surgery) has been reported to be proportional to opioid dose,[5, 9, 13] but many studies do not state dosages.

Immune suppression

The effect of opioids on the immune system relates to the presence of opioid receptors on the surface of various immune cells including natural killer cells, macrophages and dendritic cells of the innate immune system, and T and B lymphocytes of the adaptive immune system.[15, 16] In addition, opioids affect both the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system, both of which modulate immune responses,[15] which may lead to a down-regulation of the immune system with resultant immunosuppression.

Most *in vivo* studies looking at the immunosuppressive effects of opioids have been carried out in animals, or human studies with different short-term opioids after surgery, rather than patients taking long-term opioids.[17] Morphine is the most studied opioid and has repeatedly been shown to lead to immune suppression.[15] The immunological effects of opioids are many and varied, with some studies showing conflicting results and with the degree of immunosuppression differing between opioids; laboratory studies suggest that morphine, dihydrocodeine, fentanyl, methadone and codeine seem to be the most immunosuppressant whilst buprenorphine, hydromorphone, oxycodone, tramadol[15] and possibly tapentadol[17] display the least immunosuppressant effects. Tramadol and tapentadol may have less immunosuppressant effect as a large proportion of their analgesic

effect is exerted via non-opioid receptors.[17] Researchers, while confirming the impact of opioids on the immune system, highlight the complexity of interpreting data, with dose- and duration-effects currently unclear, as well as the translation of pre-clinical studies to patient populations.[15] Therefore, it is not currently possible to base the clinical choice of opioid on the immunomodulatory effects. Future clinical studies may help elucidate the significance and strength of these heterogeneous effects on patient outcomes.

The effects of opioids on the central nervous system may also contribute to impaired host defence mechanisms that can lead to increased risks of infection. For example, the depressant effects of opioids on the respiratory centre can lead to impaired coughing, and effects on opioid receptors in the hypothalamic hypocretin/orexin arousal system can cause sedation, all of which can contribute to a higher risk of lower respiratory tract infections.[15]

Importantly, for perioperative stakeholders there is now evidence that chronic opioid use is associated with increased risks of superficial and deep surgical site infections, including periprosthetic joint infection (**Table 1**).[4-14]

As well as protecting against infection, the innate and adaptive immune systems protect against cancer, with effective immunosurveillance required to reduce the risk of recurrence or metastasis. There is extensive laboratory research into the potential mechanisms in which opioid use can affect the proliferation of cancer, but this has not translated to clear clinical risk for patients.[18] Large population studies are warranted to examine this association although current evidence suggests that the fear of cancer occurrence or recurrence is not an indication to withhold opioid therapy.[18]

Endocrine and metabolic effects

Opioids have an array of effects on the neuroendocrine system and metabolism. Many endocrinopathies related to long-term and, to a lesser extent, short-term opioid use have been identified (**Table 2**).[19, 20] These are often under-recognised and can lead to adverse events. Most importantly, opioid-induced secondary hypoadrenalism may lead to a decreased stress response in patients undergoing all types of surgery, while osteopenia due to long-term opioid therapy may impact on outcomes after orthopaedic surgery (**Table 2**).

Possible mitigation of risk

Specific attribution of clear causation for many of these adverse effects on short- and long-term postoperative outcomes is not possible from the observational studies published thus far, and the extent to which chronic use of opioids before surgery directly impacts individual outcomes remains unknown. Many of the studies incorporating large cohorts of patients comprise interrogation of hospital, insurance or other administrative databases, hence may be limited by their retrospective cohort design and reliance on correct coding and data input. Even where studies controlled for some key variables including patient demographic data and pre-existing comorbidities, other variables such as patient socioeconomic status, or hospital- or surgeon-related factors, all of which could impact on patient outcomes, have not been considered.[8]

In addition, definitions and time-scales of some of the adverse outcomes vary significantly. For example, the definition of preoperative opioid use may include intermittent or regular use over variable periods (e.g., three months or 12 months) prior to surgery; and there is

also no consistent definition for the interval between the initial surgery and the time when revision surgery may be considered 'early'.

Furthermore, risk factors may be inter-related. For example, it is known that the prevalence of anxiety and depression is higher in patients taking long-term opioids,[1] including before surgery[5, 10, 11] and that anxiety, depression and preoperative opioid use are all independent predictors of early revision hip arthroplasty[4] and length of hospital stay.[21]

Nevertheless, some of the currently available evidence suggests that at least some of the risks associated with preoperative opioid use could be mitigated. For example, while much of the evidence to date about the differences between opioids and their effect on immune function comes from *in vitro*, animal or preclinical studies, it may be that changing a patient to a less immunosuppressive opioid some months prior to surgery may be appropriate[5, 8], although clinical evidence is still lacking.

There is some early clinical evidence that reducing or ceasing opioids before surgery may be associated with improved outcomes. It is clear that patients taking opioids before surgery have a higher risk of surgical site and periprosthetic joint infection, prolonged hospital stays, readmission rates, and further revision surgery after redo total hip[11] and knee arthroplasty,[10] but these risks were reduced if opioids were ceased six months before surgery.[10, 11] Similarly, the rates of surgical site infection, prolonged hospital stays, readmissions, emergency room visits, and revision surgery were higher in patients taking opioids for more than six months before surgery, but decreased to levels similar to opioid-naïve patients if opioids were ceased three months before total hip and knee arthroplasty and lumbar fusion.[6]

It is important to note that these results are observational and retrospective, indicating a patient willingness to reduce opioids, rather than randomised enforced opioid reduction or cessation. Nevertheless, preoperative opioid use should be considered a modifiable risk factor for poor outcomes after surgery, along the same lines as diabetes, morbid obesity, smoking, preoperative anaemia, and psychological comorbidities, at least for major joint replacement surgery.[3] Preoperative optimization of these risk factors, including weaning of opioid doses, may result in better patient outcomes and reduced costs after surgery.

Preoperative reduction of opioids

It is now clear that long-term opioids are neither safe nor effective for chronic pain, with side effects and complications that are worsening, not improving, quality of life.[22] Many patients presenting for surgery will have been inappropriately started on opioids previously and, irrespective of surgery, should have their opioids tapered and stopped to reduce everyday risk and improve functional outcomes. Indeed, there is evidence that tapering of opioid doses in patients with chronic pain reduces pain or maintains the same level of pain rather than leading to increased pain in the vast majority.[23]

Opioid tapering is not a simple intervention, with a recent softening of advice coming from the Centers for Disease Control[23] following concern that their 2016 guideline,[22] which proposed maximum opioid doses for chronic pain, led to abrupt tapering and cessation of opioids.[23] Many patients established on long-term, high-dose opioids have complex dependence, with opioids providing a “chemical crutch” for significant psychological co-morbidities, both predating opioid initiation and as a result of long-term opioid changes in affective processing.[24] Enforced or rapid tapering exposes these patients to risk,

precipitating mental health crises in vulnerable patients, and the danger of illicit drug seeking and suicide.[8]

Opioid tapers should be slow, achievable and patient-centred, focusing on non-opioid pain management strategies together with psychological support for the co-factors of pain.[25] This raises the issue of who should lead a pre-operative opioid taper – general practitioners may not feel confident to do so,[26] while pain services may not have sufficient capacity – and what constitutes a reasonable timescale. Identifying these patients at pre-assessment is unlikely to provide sufficient time to achieve a worthwhile dose reduction. The discussion at the initial surgical consultation should include opioid reduction as a prehabilitation goal for elective surgery,[3] with an acceptance that some patients will not be able to achieve this. The adverse effects of long-term preoperative use on surgical outcomes should be discussed as part of the shared decision-making and consent process.

Conclusion

The impact of pre-operative opioids on surgical outcomes extends beyond complex postoperative pain management. An increased risk of wound and periprosthetic infections, higher arthroplasty and spinal fusion revision rates, and longer lengths of hospital stay with higher healthcare costs may be related to the impact of long-term opioid use on immune function and endocrine systems. Weaning of opioids before surgery provides an opportunity to mitigate these risks and improve patient outcomes, but needs to be done collaboratively with the patient, primary care and pain services, and with enough time to allow gradual and manageable dose reduction.

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Table 1 Adverse effects of long-term opioid therapy on short- and long-term post-surgical outcomes

Operation type	Outcome
Hip and knee arthroplasty – primary[4-6, 8]	Increased risk of surgical site and periprosthetic infections Increased rate of early revision arthroplasty Prolonged hospital stay Greater likelihood of non-home discharge Higher readmission rates Higher healthcare costs (from before admission to up to one year after discharge)
Hip and knee arthroplasty – revision[10, 11]	Increased risk of surgical site and periprosthetic joint infection Prolonged hospital stay Greater likelihood of non-home discharge Higher readmissions rates Higher number of post-discharge emergency department visits Increased risk of further revision surgery
Shoulder arthroplasty[12]	Increases in surgical site and periprosthetic joint infections Prolonged hospital stay Greater likelihood of non-home discharge Higher readmission rates Higher number of post-discharge emergency department visits Higher healthcare costs
Spinal surgery[6, 7, 13]	Increased risks of wound complications (including surgical site infection) Higher readmission rates Higher number of post-discharge emergency department visits Higher lumbar and cervical fusion revision rates Prolonged hospital stays Higher healthcare costs
Elective abdominal surgery[9]	Prolonged hospital stays Higher readmission rates Higher inpatient and postoperative costs Greater likelihood of non-home discharge
Lower extremity bypass surgery[14]	Higher rates of surgical site infection Prolonged hospital stay Higher hospitals costs

Table 2: Major endocrine and metabolic effects of opioids

Hormone/hormone complex	Effect	Duration of treatment	Clinical effects	Comments
Hypothalamic-pituitary-adrenal axis	Inhibition of corticotropin-releasing hormone (CRH) secretion, resulting in decreased adrenocorticotropic hormone (ACTH) release Possible direct inhibitory effect on adrenal function	Inhibitory effects seen with both short-term and long-term use Effect size may be dose-related	Low basal blood cortisol levels Clinical significance of these findings not clear Instances of Addisonian crises have been reported	Glucocorticoid therapy may be necessary Impaired stress response may lead to intraoperative and postoperative hypotension
Hypothalamic-pituitary-gonadal axis	Inhibition of gonadotropin-releasing hormone secretion from the hypothalamus and subsequently the secretion of gonadotropins (luteinising hormone and follicle stimulating hormone) from the pituitary gland.	The suppressive effect begins as soon as the drugs are administered and cessation results in axis recovery. Also seen with long-term use	Bone loss, decreased libido, infertility, and depression in both sexes Erectile dysfunction, impotence, and decreased muscle mass in men. Oligomenorrhoea and amenorrhoea in women.	Androgen deficiency more likely with long-acting opioids than short-acting ones (may be related to duration of effect) The typical opioids tapentadol and buprenorphine may result in milder or no suppressive effects
Bone metabolism	Reduction in bone mineral density indirectly, by causing hypogonadism, and directly, by inhibiting osteoblast activity	Long-term use	Osteopenia Osteoporosis Fractures	Other risk factors for decreased bone mineral density and osteoporosis include poor nutritional status, hypogonadism, inhibition of osteoblasts,

	osteocalcin synthesis and so affecting bone turnover			decreased osteocalcin synthesis, abnormal calcium and parathyroid hormone and increased bone resorption There is an increased risk of bone fracture in patients on opioids, which may also be related to falls and reduced mobility
Body weight and insulin	Chronic opioid use is associated with weight gain, hyperglycaemia and worsening diabetes mellitus	Long-term use	Role in regulating food intake and food choice, reward associated with taste Weight gain Insulin resistance Diabetes mellitus	May be a central action via the sympathetic nervous system and impaired insulin secretion Hypogonadism is also associated with increased insulin resistance

Data summarised from Seyfried et al.[19] and Fountas et al.[20]
Effects on growth hormone, prolactin, anti-diuretic hormone, oxytocin and thyroid hormones are variable or less pronounced and there is no good evidence linking them to adverse post-surgical outcomes. Therefore, they have not been included in the table.